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BENIGN TUBERCULOUS INFILTRATION OF THE LUNG (EPITUBERCULOSIS)

BY

J. C. SPENCE, M.D., F.R.C.P.

(From the Babies' Hospital and Royal Victoria Infirmary, Newcastle-on-Tyne.)

The following observations may throw some light upon the condition described as epituberculous infiltration or epituberculosis, a condition which probably is not different from that formerly described as tuberculous splenopneumonia, Frühinfiltrat, or tuberculose inflammatoire.

It is difficult to define exactly the term epituberculous infiltration for it is used to denote a variable clinical picture, of which the underlying pathology is not known through lack of opportunity for post-mortem study. It was first used in 1920 by Eliasberg and Neuland to describe a benign clinical syndrome in a tuberculous child, of which the chief features were an extensive dense consolidation of the lung revealed by percussion, auscultation, and X-ray examination; a harsh cough without sputum; an absence of severe constitutional symptoms; an absence of an initial acute illness; a slow disappearance of the consolidation, without signs of softening or cavitation; a complete recovery without fibrosis or bronchiectasis. The nature of the lesion is considered by many to be an allergic reaction around a small primary tuberculous focus, but this has been deduced by speculation and not proved by pathological investigation. The argument that has been advanced in favour of this theory is that, were the whole lesion a caseous tuberculous process or gelatinous pneumonia, the illness would be more severe, the course of it less benign, and the result less satisfactory.

The three cases to be described had that combination of an extensive solid lesion of the lung, with relatively slight symptoms of illness, which justifies their being regarded as examples of children suffering from epituberculous infiltration of the lung. They were presumably tuberculous children, the skin tuberculin reaction being positive, and in two there was a definite history of contact. From none of them were tubercle bacilli recovered in the sputum or stomach washings. In the third a further investigation was pursued by exploring the lung lesion and examining the material obtained in the aperture of the exploring needle. This was done twice at an interval of four weeks, and in two sites. On both occasions tubercle bacilli were present in the material. This placed the tuberculous nature of the process in this case beyond doubt and the evidence suggests that the whole lesion in so-called epituberculous infiltration is a caseous tuberculous process, yet producing no severe constitutional symptoms.

Case reports.

The details of the three cases on which this communication is based are as follows:—

Case 1. A girl, R. G., 6 months old, came for the first time under observation on November 14th, 1927. She had not gained weight for two months and it was for this reason that advice was sought. For nearly three months the child had been coughing but there had been no other symptoms.

The father was a man of 21 who had been in poor health for a few years. On examination it was found that he had active pulmonary tuberculosis with tubercle bacilli in the sputum. The mother was healthy. There had been one other child, who had died a year earlier of tuberculous meningitis.

The child was pallid, thin, and weighing 10 lb. She was not ill. She looked contented and happy, and the face itself was fat. On examination there was a pronounced dullness of the right thorax from the apex to the third intercostal space in front, and to the mid-scapular level behind. The note was equally dull in the upper part of the axilla. Over this affected area the respiratory murmur was diminished to a degree suggesting a pleural effusion. Distant tubular breathing could be heard, but there were no râles or rhonchi. At the base of the lung the percussion note and air entry were normal. The signs over the left lung were normal.

The abdomen was not protuberant: liver and spleen not enlarged. The urine was free from cells, albumin and sugar. The heart was normal and not displaced. The skin, glands, mouth and naso-pharynx were normal. Hæmoglobin = 65 per cent. Rectal temperature normal. Skin tuberculin reaction to ·1 c.cm. of a 1 in 1000 dilution was strongly positive, the reaction lasting ten days.

The existence of a localized empyema was considered possible, so an exploring needle was put into the second interspace in front and behind. No pus or fluid was found. A small amount of caseous material was present in the aperture of the needle's point, but this was not examined microscopically.

The child was kept in hospital for 10 months and remained happy and contented without symptoms of illness. For the first three weeks the temperature was normal. Then followed a bout of fever rising to 102° for 10 days. There was no alteration in the signs in the lung during this fever. Apart from this the child was afebrile throughout her stay, except for two or three rises of temperature for single days which were attributed to ward infections. There was no gain in weight for the first three months. Thereafter there was a steady gain. At the age of 12 months the weight was 12 lb.; at 15 months 14½ lb.; at 16 months 15½ lb.

The signs in the lung remained unaltered during her first three months in hospital. In February, 1928, (child then 9 months) the dullness of the percussion note over the right upper lobe began to diminish, and the respiratory murmur became more pronounced. This improvement continued. A slightly impaired percussion note could still be detected in September, 1928, (age 16 months) when the child was discharged, but the air entry to the upper lobe was normal.

The skin tuberculin reaction was repeated three times with ·1 c.cm. of a 1 in 10,000 dilution and on each occasion gave a positive reaction of several days duration.

On discharge the child was small and underweight, but was well covered with subcutaneous fat, and looked perfectly healthy. A year later at the age of 2 years, 4 months she was in good health, weighed 21½ lb., and was without cough. There was no splenomegaly, and no signs of disease could be elicited by auscultation or percussion.

In May, 1930, at the age of 3 she was a healthy looking child of 26 lb. without sign or symptom of disease. In November, 1931, at the age of 4½ years she was again in good health, and appeared to be completely cured.

A series of X-ray examinations was made and Figures 1, 2 and 3 are chosen from these to illustrate the X-ray appearance of the lesion, and the mannner and rate of its disappearance. After admission the size and density of the shadow remained

unaltered for about 4 months. Fig. 1 (February 2nd, 1928) shows it at this stage. Fig. 2 shows the shadow as it was on August 11th, 1928, 9 months after admission; Fig. 3 on September 4th, 1929, a year after discharge. A later picture taken in June, 1931, shows that the shadow has completely disappeared. The consolidation lasted for about 2 years. When disappearing it receded first from the periphery of the lung.

Case 2. E. T., girl, aged 5 years admitted to hospital on March 5th, 1930. She first attended as an out-patient with the complaint of lassitude and pallor. She had had no recent acute illnesses.

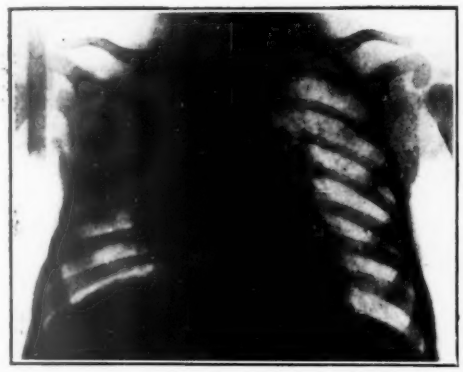

FIG. 1. Case 1. (Feb. 2, 1928). Skiagram taken 3 months after admission, showing the lung shadow as it persisted for the first four months.

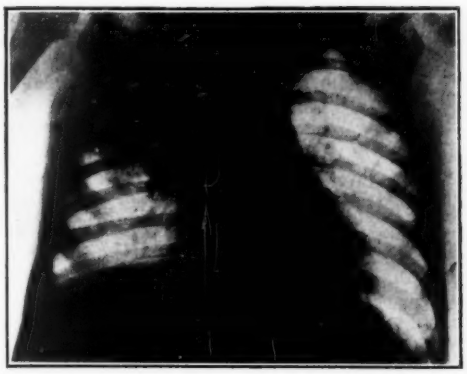

FIG. 2. Case 1. (Aug. 11, 1928). Skiagram taken 6 months later.

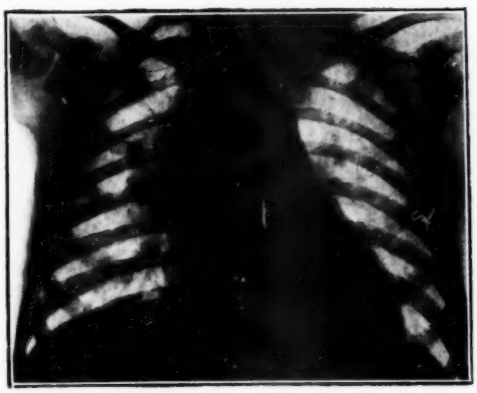

FIG. 3. Case 1. (Sept. 4, 1929). Skiagram taken a year after discharge from hospital.

In the family there was no definite evidence of tuberculous infection, but younger child aged 1½ years had died some time before of meningitis believed to have been tuberculous.

The child was small but fairly well nourished. Weight 28½ lb. She had no apparent symptoms and co-operated cheerfully and readily in the examination. She looked so healthy that it was suprising to find signs of a dull area over the whole of the upper part of the right lung. This was evident both in front and behind, and the signs of dullness with suppression of breath sounds suggested a localized pleural exudate. The area was explored by a needle and no fluid or pus obtained. The skin tuberculin reaction was strongly positive. X-ray examination revealed a dense area

corresponding to almost the whole of the upper lobe with the lower limit sharply defined in its outer part (see Fig. 4).

From March, 1930, until January, 1932, she was kept under constant observation as an in-patient of the hospital, an later of Stannington sanatorium under the care of Dr. T. C. Hunter. During this time she continued in good health. There was no fever whatsoever: no cough and no sputum. She gained weight and at the age of 7 she weighed 41 lb.

The consolidation of the right upper lobe began to disappear about three months after coming under observation. The rate of disappearance was slow, signs of dullness

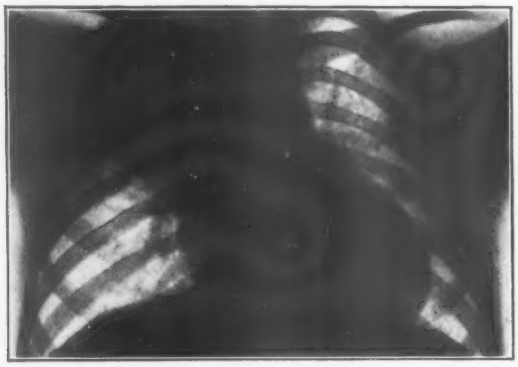

FIG. 4. Case 2. (March 17, 1930). Skiagram taken shortly after admission.

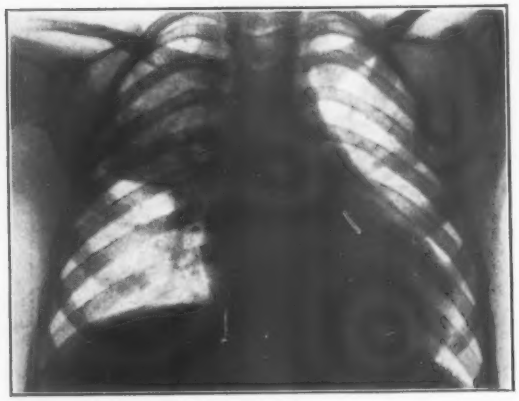

FIG. 5. Case 2. (July 23, 1930). Skiagram 4 months later.

being still evident for more than a year. At no time was there any softening of the focus or evidence of cavitation. By January, 1932, all signs had disappeared and she looked in perfect health.

A series of X-ray examinations showed a slow diminution in the size of the shadow receding from the outer margin of the lung (see Figures 4, 5, 6, 7). The last of these (Fig. 7) taken on October 30th, 1931, shows only an increased hilum shadow on the right side compared with that on the left.

The signs and X-ray appearances of consolidation in the lung were in this child very similar to those in the first case, but disappeared more slowly.

Case 3. A boy, W. S., aged 7 months, admitted to hospital on July 3rd, 1931. Brought for advice because of dyspepsia and failure to gain weight.

The mother died of pulmonary tuberculosis 9 weeks before the child was admitted. She had been in daily contact with him for the first three months of his life, and during this time she had had fever, with abundant sputum, containing tubercle bacilli. The father was apparently healthy. There were four other living children aged 14, 13, 11 and 6 years. A child aged 2 died at about the time of the birth of this child. The cause of death was unknown.

The child was small and underweight, 9½ lb. He was lively and contented. The abdomen was protuberant, but not distended. His appearance suggested a condition of dyspepsia due to lack of care and proper feeding.

FIG. 6. Case 2. (Oct. 27, 1930). Skiagram.

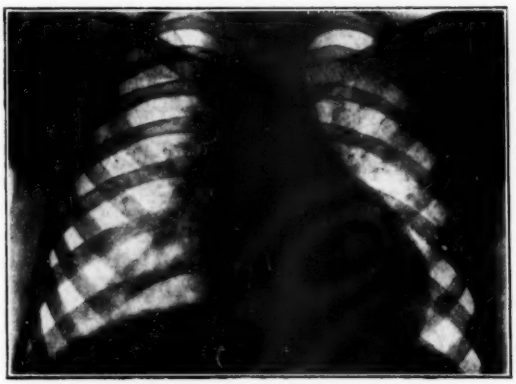

FIG. 7. Case 2 (Oct. 30, 1931). Skiagram 18 months after FIG. 4.

On examination pronounced dullness was found over the upper part of the left lung. This was very evident in front and in the axilla, and less pronounced behind. The area of dullness extended down to the nipple. The breath sounds were diminished in that area and there was complete absence of crepitations and râles. On listening to the forced respiration provoked after crying slight wheezing rhonchi could be heard distantly, otherwise there were no adventitious sounds.

The right lung was normal. The heart was not displaced. The spleen was enlarged two fingers breadth before the costal margin. Liver not enlarged. The skin was moist and clear. Glands palpable on both sides of the neck down the sterno-mastoids. Mouth and throat clean.

The temperature was normal. The urine contained a faint trace of albumin but no cells.

Skin tuberculin reaction was strongly positive to ·1 c.cm. of 1 in 1,000 dilution. Hæmoglobin 60 per cent. Leucocytes = 11,600.

The X-ray examination (Dr. Whately Davidson) on July 8th, 1931, showed a dense shadow of the upper and middle part of the left lobe (Fig. 8). The shadow diminished in intensity at the apex, and the base was clear. The diaphragm moved normally.

A diagnosis of tuberculous infiltraton of the lung was made. For the next two months there was a rapid improvement in his general condition but the signs in the chest were unaltered. A note made on September 4th, 1931, reads ' The signs and symptoms are those of a so-called epituberculosis. He has been in hospital 2 months and gained 3 lb. Still underweight, but quite happy and symptomless. He feeds well, smiles and is contented. Temperature usually below 99°, and occasionally reaches 100°, but no bouts of fever. There is no cough, but Sister has noted periods of slight wheeziness lasting an hour or two. In spite of the absence of symptoms a big massive lesion persists in the upper part of the left lung, unaltered since admission.'

FIG. 8. Case 3. (July 8, 1931). Skiagram taken shortly after admission, aged 7 months.

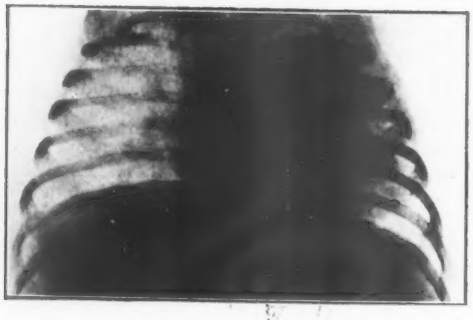

FIG. 9. Case 3. (Oct. 19, 1931). Skiagram taken 3 months later: patient afebrile and gaining weight.

On September 7th the chest was explored. A needle was inserted into the third interspace in the mid-axillary line. No pus or fluid was obtained. A small amount of caseous material obtained in the needle was collected for examination. Two slide preparations were made. Each contained tubercle bacilli. A guinea pig was inoculated with the material. Killed 5 weeks later it showed typical tuberculous lesions from which the bacilli were again recovered.

Four weeks later, on October 9th, 1931, a second exploration was performed. The needle was introduced in front in the mid-clavicular line in the third interspace and directed medially, so that the point of contact with the lung should be as far removed as possible from the site of the previous puncture. No pus or fluid was obtained. A small amount of necrotic material was again found in the needle. This was examined in two slide preparations and again tubercle bacilli were present.

The child has remained in hospital and has now been under observation for 6 months. The present weight (January 6th, 1932) is 13 lb. 2 oz. During the past six weeks the weight has been stationary. Splenomegaly persists. The general general condition improves. In November and December (5th and 6th months of sojourn in hospital) the glands in the neck increased in size but these are now subsiding.

A second X-ray examination (Fig. 9) on October 19th, 1931, shows the dense shadow persisting, but diminishing in size, receding from the periphery. A third X-ray on January 6th, 1932, shows no further change.

Discussion.

The chief point of interest in these three cases is that clinically they resembled each other in being tuberculous children, each with a massive lesion of the lung which was benign in character and lasted for a year or more, without much disturbance of the general health beyond some pallor and loss of weight in the early stages.

In the first two the evidence that the lesion was tuberculous was only presumptive. In favour of this view there are the facts that both had positive skin tuberculin reactions, and one a history of contact with a tuberculous parent. Any other explanation of the nature of the consolidation is difficult. The children had not had pneumonia, and the complete disappearance of the lesion after it had been present for a year, and the recovery of the lung without signs of fibrosis or bronchiectasis, exclude bronchial obstruction as the cause.

Görter and Lignac have published a paper under the title ' Collateral inflammation of the lung round a tuberculous centre ' in which they report the case of a girl of 3 years with a dense shadow in the right lung from which they recovered tubercle bacilli by lung puncture. They were able to obtain a post-mortem examination 18 months later, by which time the dense lesion had greatly decreased in size. They put forward the view that the most probable explanation of the process was that from a small caseous focus there spread a collateral inflammation over the largest part of the affected lobe, and that an acute infection with pneumococci played an important role in this process. But in the present cases there was nothing to suggest or prove a recent pneumococcal infection.

The third case recorded above was infected at a very early age, shortly after birth, so the failure to gain weight in the first six months of his life had had a more evident effect on his general condition. Otherwise the physical signs of the lesion and his progress resembled those in the first two cases. In this third case the tuberculous nature of the process has been proved beyond doubt by recovery of tubercle bacilli directly from the lung at two sites and on two occasions. The first exploration was made at a point which

might conceivably have been the primary tuberculous focus, small in size and central in site. The second exploration was made at a point near the periphery of the consolidated area, as far as possible from the point of the first exploration. Tubercle bacilli were obtained in equal number and with equal facility from both parts of the lesion. It is clear, therefore, that in this case we have an infant infected shortly after birth with a large tuberculous lesion affecting almost the whole of the upper half of the lung, yet causing comparatively little disturbance to his health and no fever, and permitting a gain of weight.

Conclusions.

This communication draws attention to the value of careful examination of material obtained in the syringe needle when exploring the chests of cases of this type.

Of the cases which are described the chief point of clinical importance is that they demonstrate that even a young infant has a great power of recovery from tuberculous lesions of the lung, a view which Armand-Delille and others[3] have maintained for some years.

REFERENCES.

1. Eliasberg, H., & Neuland, W., *Jahrb. f. Kinderh.*, Berlin, 1920, XCIII, 88.
2. Görter, E., & Lignac, G. O. E., *Acta Pædiat.*, Stockholm, 1930, X, 87.
3. Armand-Delille, Vibert, J., & Pannier, P., *Rev. franc., de Pédiat.*, Paris, 1927, III, 1.

RICKETS IN SYDNEY, AUSTRALIA,

BY

KEMPSON MADDOX, M.D., M.R.C.P.,

Assistant Physician to the Royal Prince Alfred Hospital, Sydney;

Late Physician to Out-Patients, Renwick Hospital for Infants, Sydney.

This contribution, originating from an impression of the frequency of minor rachitic manifestations among the children of the public hospital class in Sydney, records the result of an examination conducted towards the end of the winter of 1929. Search was made for evidence of rickets in 218 consecutive infants admitted to the Quay Street out-patients' department of the Renwick Hospital for Infants, Sydney, whose ages fell between six months and two years. The reasons for attendance were, in most cases, minor catarrhal disorders, feeding difficulties, simple ear and skin troubles, or for food relief. No selection of cases was made, and no child was seriously ill.

Enquiry was made into the social condition of the family, including the type of dwelling, location, father's wage, and number of other children in the family. The present and previous health, and progress, of the patient were noted, and details taken of the dietetic history, including the nature, amount and period of administration of anti-rachitic foods and drugs. In the case of breast-fed infants, an attempt was made to assess the satisfactoriness or otherwise of the mother's diet from this standpoint. The child was then specifically examined for evidences of rickets, and in 129 unselected instances, a radiogram of the wrist was taken.

Clinical standards.—It is necessary at once to define the clinical points which were considered as abnormal in the present investigation.

Feeding. A theoretical deficiency of vitamin D was attributed to infants reared wholly on dried or condensed milk or biscuits, from birth or for a period of four months or more preceding the examination, without the addition of any fresh cow's milk or cod liver oil. Cases where these additions had been made less than two months previously were also included; also, where enquiry showed that the mother had had little or no fresh milk, eggs, or butter, or where breast-feeding for economic reasons had been persisted in for more than 12 months. In older children, a father out of work with two or more other children to be fed, precluded a sufficiency of fresh anti-rachitic foods.

Previous health. The occurrence of convulsions was particularly noted. The term ' catarrhal illness ' does not here include pertussis, which was very prevalent at the time.

SYMPTOMS. Under this title in the following pages nocturnal restlessness, sweating of the head, and general irritability are meant.

DELAYED PROGRESS. Delay in dentition beyond eight months, and failure to walk by fourteen months, were considered as abnormal.

SKULL CHANGES. Persistence of patency of the fontanelle beyond eighteen months, indubitable bossing or an unusual squareness or disproportion in size to that of the trunk (Fig. 1), persistence of the interfrontal suture, craniotabes or natiform cranium, together or separately, were the standards taken.

FIG. 1.

HARRISON'S SULCUS. This is here taken to include all degrees of splaying and eversion of the lower ribs. Other rarer chest deformities, e.g., parasternal depression, are included for convenience under this heading (Fig. 2).

ENLARGEMENT OF THE COSTO-CHONDRAL JUNCTIONS. This has been almost a matter of individual taste in many cases. For the present purpose, it was termed ' marked ' when the knobs were rounded and distinct enough to be either visible, or plainly felt with the flat of the hand. ' Slight '

enlargement required the pulps of the fingers to be rubbed along the ribs for its clear definition. The ' sharp ' type, like a knife edge, associated with splaying of the ribs, was also included in the latter category.

LIGAMENTOUS LAXITY. This is associated in the majority of instances with muscular hypotonia. The following plan was adopted in order to have a rough standard for comparison. The observer stands to the right of the child, who sits on a table or chair, and firmly presses the child's lower limb against his own with the left hand, so as to secure absolute immobility, while

FIG. 2.

the right hand grasps just above the child's ankle and preserves full extension and at the same time rocks the leg laterally. If the ankle moves through a lateral excursion of one inch or more, the result is labelled as ' marked,' and lesser degrees ' slight ' or ' moderate.'

POT-BELLY. This was only ascribed to the child when there was an approximate angle of 150° or less at the xiphisternum on viewing the lateral abdominal profile with the child sitting up, associated with diastasis of the recti and somtimes an umbilical hernia. Enlargement of the liver had to be

quite definite, usually about two fingers breadth below the ribs at Murphy's point. Rachitic kyphosis is frequently a factor in the production of abdominal fullness (Fig. 3).

ANÆMIA. Anæmia and abnormalities in body weight were noted when very marked.

WRISTS. The distal extremity of the radius was invariably examined for any increase in circumference.

The clinical diagnosis.—In this series a positive clinical diagnosis was made in the presence of two or more of the following features:—Symptoms,

FIG. 3.

history of convulsions, delay in dentition or walking, or both, skull change, definite Harrison's sulcus, marked beading, marked ligamentous laxity, marked pot-belly with enlarged liver, all judged strictly according to the standards above described.

The term ' clinically positive ' includes patients with evidences of either past or present disease. As it is impossible to tell with accuracy which phenomena are characteristic of either phase.

The radiographical diagnosis.—The radiograms were snapped with a Phillips's portable Metalix outfit with the wrist held immobile on the plate, palm downwards. No selection whatever was made of the cases for radiography, the only reason that the whole series of patients could not be done was that the machine and operator were not always available or that the mother would not wait for this purpose.

Evidence taken as indicating healed rickets, consisted of a curved zone of sclerosis sometimes surmounted by parallel transverse lines extending into the shaft, but in which the ' wine glass ' ulnar concavity of the active lesion had been filled in. More commonly, a wool-like radio-opaque zone capped the extremities of both bones, for a depth of several millimetres. This was frequently deeper on the inner (ulnar) side of the radial extremity than on the outer aspect, and had a blurred junction with the shaft, which, as the bone grows and the lesion heals, becomes sharper and finer, so that it ultimately appears on the radiogram as if the distal borders of the normal radius and ulna had been outlined in white ink. All grades of these appearances occurred right down to the unquestionable normal, but for the present purpose only those cases have been included which are just as unquestionably abnormal.

The radiograms labelled ' active ' were of the type where definition of the trabeculæ disappeared in the last half-centimetre of the ulna, and was replaced by an increasingly blurred but relatively translucent zone. The classical ' wine glass ' or ' florid ' extremity was seen but rarely, and even if it possessed a sclerosed border but was not filled in and square, a certain degree of activity was assumed. Relative shortness of the ulna appeared more frequently in otherwise normal pictures, and an extraordinary degree of ' beaking ' was often unassociated with other noteworthy features. Well-defined changes at the wrist were often reflected by the ends of the metacarpals. No curving or green-stick fracture was observed in any picture.

The number and size of the carpal centres and radial epiphysis were noted, but bore no constant relationship to the above classification. Table 3 gives the average age for the appearance of each centre in the radiographically positive and negative groups. It will be observed that the difference in mean age of appearance of these centres is very slight and therefore of no value either individually or collectively for the purposes of diagnosis, at least as far as this series of cases goes. The only other point which seems worthy of note in this connection is the much earlier time of appearance of the radial epiphyseal centre in the whole series as compared with those set down in the standard anatomical text-books.

Clinical results.—Of 218 patients, 116 (52 per cent.) were adjudged to show unmistakable evidence of rickets, past or present. This was made up of 67 out of 129 radiographed cases (=52 per cent.), and 49 out of 89 unradiographed cases (=53 per cent.) (Table 1).

As regards age distribution, positive clinical findings were noted in 36·7 per cent. of those between six and nine months; in 77 per cent. of those between nine and twelve months; and in 50 per cent. of those between twelve months and two years.

As an example of a typical clinically ' positive ' case, the following case notes, selected at random, may be quoted:—

D. H., aged 18 months, male. Two other children in the family; father not working, lives with rest of family in one room in Surry Hills. Breast fed at first for 3 months, then put on to dried milk. Since 12 months old has had ' anything,' but no cod-liver oil. First tooth appeared at 8½ months accompanied by bronchitis. Cannot walk properly yet, but can stand holding on to chair. Child is pallid and flabby, fairly well nourished, has three transparent-looking teeth, slight anæmia of mucous membranes, very soft muscles and moderately lax ligaments; the head appears large and square, fontanelle almost closed. The chest shows a slight Harrison's sulcus and marked beading. There is well marked abdominal enlargement and the liver is plainly enlarged.

This may not be a typical text-book picture, but there is no room for doubt as to the diagnosis. The only uncertain point is whether these signs mean past or present disease.

The characters and frequency of the clinical features on which a diagnosis was based can now be considered in more detail (Table 1).

1. Symptoms. The usually accepted symptoms of activity such as sweating of the head, restlessness and irritability, are not of much assistance as one is forced to rely on the uncertain grounds of a mother's impressions and her temperamental reaction to her child's behaviour. Generalized tenderness as a symptom is a relict of the days of Barlow's disease. A clear history of recent convulsions or a positive Chvostek sign is much more helpful. In this group the latter was not sought for, and the former is noted seven times. Symptoms of activity such as the above were prominent in 18 cases only.

2. Previous health. Illnesses of a catarrhal character had occurred in 84 instances (39 per cent. of all cases). Bronchitis (especially at teething time), frequent colds, broncho-pneumonia, gastro-enteritis, measles and pertussis appear most frequently. Erythrœdema appeared four times, a rather high incidence, and in two cases associated with clinical rickets.

3. Delay in dentition was seen in 45 per cent. of cases in a total of 185 infants old enough to manifest it. Qualitatively, the general average was poor, many teeth being small, irregular and already carious. Departure from the usual order of appearance was common. One tooth would perhaps appear before eight months, followed by a delay in some cases of six months before the next erupted. There were no noteworthy changes in the development of the jaws. Delay in walking was apparent in 40 of 97 infants old enough to show it. As is usual, these children included those with the most hypotonia and looseness of the knee ligaments,

TABLE I.

STATISTICAL SUMMARY OF THE INQUIRY.

Detail.	Whole series.		Radio-positive group.			Radio-neg. group.	Unradio-graphed group.
	Cases.	Per cent.	Active.	Doubtful.	Healed.		
CASES:							
Total	218	100	16	7	40	66	89
AGE:							
6 to 9 months ...	52	25	7	2	8	21	14
9 to 12 ,, ...	48	23	7	2	5	13	21
12 to 24 ,, ...	118	52	2	3	27	32	54
FEEDING:							
Breast milk	104	48	6	3	21	31	43
Dried ,, ...	84	39	8	3	10	26	37
Fresh ,, ...	75	35	2	3	10	26	34
Cod-liver oil	67	30·7	7	2	17	13	28
Vitamin D. deficiency in	94	43	7	2	15	26	44
PREVIOUS HEALTH:							
Convulsions	7	3	0	1	2	2	2
Catarrhal infections ...	84	39	6	5	14	31	28
SYMPTOMS:							
(vide text)	18	8	1	1	4	3	9
SIGNS:							
Delayed dentition .	86/185	45	8/16	4/5	20/32	22/55	32/76
,, walking ...	40/97	41	0	1/2	6/20	15/33	18/42
Skull changes	49	22	5	0	2	15	27
Indefinite wrist enlargement	54	25	10	5	5	10	24
Harrison's sulcus ...	55	25	4	2	11	21	17
Slight beading to moderate	114	52	7	4	30	31	42
Marked beading ...	57	26	9	1	8	20	19
Slight hypotonus ...	130	60	5	6	21	46	52
Marked ,, ...	39	18	10	1	5	14	9
Pot-belly	90	41	8	4	14	34	30
Enlarged liver	26	12	8	1	4	6	7
GENERAL CONDITION:							
Much overweight ..	33	14	6	0	5	8	14
,, underweight ...	18	8	1	0	3	7	7
Marked anæmia... ...	22	10	1	0	5	4	12
CLINICALLY POSITIVE ...	116	52	13	5	18	31	49

4. Skull changes, strictly of the type defined above, were observed in 22 per cent. of the children, but a squareness of the head, not exceeding the normal maximal circumference, was far commoner than this. Persistence

of the fontanelle beyond 18 months was the largest factor in these head-positive cases. Natiform cranium was seen once only. Craniotabes though repeatedly searched for was never discovered, perhaps because, as De Buys[1] and other observers have stated, it is more frequently found for a time under the age of six months. The box-like largish head is a familiar sight in the out-patients' waiting room.

5. Epiphyseal enlargement, especially of the wrists, was not encountered in this series. In about 25 per cent. of instances there was a suspicious bulging of the lower radial extremity, on stretching the skin over the dorsum of the wrist, but this occurred almost invariably in the fat overweight child and the soft tissues were probably for the most part responsible for the apparent enlargement. Beading of the fingers, as described by Thomson, was observed in two cases only.

6. Harrison's sulcus was present in various degrees in a quarter of the cases. Rarely, other forms of chest deformity such as pigeon breast, lateral flattening and parasternal depressions were seen.

7. Enlargement of the costo-chondral junctions or rib beading was a definite feature of this series. It was found in a slight to moderate degree in half the children examined and to a definite, marked, or decided degree in a further quarter, though owing to the super-normal thickness of the fat in most of the patients it was visible in three only. One case of spurious beading of the scorbutic type was met with.

8. Ligamentous laxity was also very common, being slight to moderate in 60 per cent. and marked in 18 per cent. of all patients. In practically all cases the laxity was directly proportioned to the degree of muscular hypotonia.

9. Abdominal enlargement was observed to the specified degree in 41 per cent. of patients, usually in association with a mild grade of diastasis of the recti, and in 12 per cent. of the series with a readily palpable enlargement of the liver. Umbilical hernia was not a common feature, nor was splenomegaly found in any child.

10. Anæmia of an indubitable character was only noted in 22 cases. The general state of nutrition was on the whole good. Thirty-three babies were excessively over-weight and many more exceeded the normal for their age, particularly those reared on dried milk according to the directions on the tin. Such children were pale, with a tight but non-pitting type of flesh the firmness of which often contrasted with lax ligaments and muscles, by which the limbs could be placed in all kinds of unnatural postures. Many breast-fed babies were also over-weight but had rosy cheeks and firm ligaments.

Radiographic results.—The whole series can be divided into two groups according to whether or not a picture was taken. Technically unsatisfactory or ruined negatives were rejected, which left 129 pictures to be reviewed. This was done quite independently of the clinical result.

Tables 1 and 2 indicate the gross and detailed results respectively of this examination. In 66 instances (51 per cent.) no alteration was visible. The distal extremities of ulna and radius were square and sharply cut. There was not splaying or osteoporosis. The internal detail of the metaphyses remained clear and sharp. The metacarpals were equally free from change. Definite florid rickets appeared 16 times, i.e., in 12·4 per cent. of the rayed cases. There were 7 borderline cases in which it was impossible to be sure of the activity of the lesion, though one undoubtedly existed. Examples of healed rickets of all grades were noted 40 times, making a total incidence of 49 per cent. among the rayed cases, of all types of positive lesion. All patients with active disease were below the age of fourteen months.

TABLE 2.

RELATIONSHIP BETWEEN RADIOGRAPHIC AND CLINICAL RESULTS.

Series.	Total.	Radiographically positive.		Clinically positive.	
		No.	Per cent.	No.	Per cent.
Radiographed ...	129	63	50	36	28
Unradiographed ...	89	—	—	49	53

Comparison of clinical and radiological results.—It is usually accepted that no one or more clinical signs can be relied upon as indicating the degree of activity or stage of healing of a rachitic process. Only a radiogram or an estimation of blood phosphorus and calcium can determine this with certainty. Nevertheless, clinical signs are held to precede radiographic changes in order of appearance. Again, certain clinical signs such as bossing of the skull, beading of the ribs and laxity of the ligaments, will remain after radiographic cure has occurred, while deformities as bent bones and Harrison's sulcus will remain as land marks throughout life.

A perusal of the literature shows the remarkable difference in significance attached to individual symptoms by authorities in different centres, and this suggests that rickets has a varying symptomatology in different parts of the world. Aidin[2] holds this view. He also thinks that in different localities the clinical and radiographic signs of rickets can vary in order of appearance as well as frequency. Unanimity exists on some points, e.g., that a slight degree of rib-beading, pot-belly or sweating should not be too much stressed, and that no significance should be attached to slight splaying or osteoporosis in the radiogram, or to slight degree of delay in passing the various milestones in development. Craniotabes and epiphyseal enlargement seem to be among the most variable signs. Hess[3], whose experience in this subject is perhaps unique, states that in New York beading of the rib junctions is

positive before the radiogram. In London it is considered that radiographic signs may precede epiphyseal enlargement by three to four weeks. As Pearson[4] says, ' the interpretation of the earliest changes both clinical and radiographic becomes a matter of individual opinion,' and apparently must be worked out for each locality. In any such enquiry as the present, therefore, it is necessary to define the standards used as clearly as possible as has been attempted here.

TABLE 3.

MEAN AGE IN MONTHS AT WHICH CARPAL AND RADIAL EPIPHYSEAL CENTRES WERE OBSERVED.

Centres present.	Radio-positive (all types)	Radio-negative.	Normal (from Cunningham's Anatomy).
None	—	11	—
1 for carpus 0 for radial epiphysis	9	13	11–12
2 for carpus 0 for radial epiphysis	12	11·5	12–14
for carpus 0 for radial epiphysis	13	13	24
1 for carpus 1 for radial epiphysis	—	6	24
2 for carpus 1 for radial epiphysis	15	14	24
3 for carpus 1 for radial epiphysis	16	16	24

PRESENT SERIES. Tables 1 and 2 afford a gross and detailed comparison between clinical and radiographic results in the present series. Though approximately half the whole series were clinically positive, and half the rayed series radiographically positive, only 28 per cent. of the latter could be classed as positive according to clinical standards. This suggests that signs of healed rickets persist in the radiogram longer than clinical signs of a multiple and diagnostic character, or that a positive radiogram is to be frequently found in the absence of adequate clinical signs. The former explanation is the correct one, as of 40 cases with X-ray signs of past disease only 18 would have been suspect on clinical grounds. Of 16 radiographically active cases, 13 were adjudged as clinically positive. The clinical signs in these 16 cases were as follows: Delay in dentition, 8 cases (none were old

enough to show any delay in walking); skull changes, 5 cases; Harrison's sulcus, 4 cases; marked rib beading, 9 cases; slight rib beading, 7 cases; slight muscular and ligamentous laxity, 7 cases, marked in 9 cases; abdominal and hepatic enlargement, 8 cases. Six infants were grossly over weight, and one anæmic and one marasmic.

TABLE 4.

ILLUSTRATING VARIATION IN SYMPTOMATOLOGY IN CERTAIN CENTRES.

City.	Approx. sunshine.	Observer.	Year.	Mode of exam.	Incidence (percent.)	Beading.	Epiph. enl.	Craniotabes.
London ...	+	Still ...	1908	Clin. ...	40	Unimportant	Early, common	Freqt. & late
		Paterson ...	1925	Clin. & X ray	1·2 (active) 32 (healed)	—	—	—
		Mackay ...	1926	Clin. & X-ray	8 (active)	—	—	—
Manchester	+	Chisholm ...	1926	Clin. & X-ray	26	—	—	—
Liverpool ...	+	Aidin ...	1927	Clin. & X-ray	95	Sl. enlargemt. diagnostic	Rare	V. rare
Edinburgh	+	Thomson ...	1900	Clin. ...	50	Marked & constant	Common	Common first sign
New York ...	+	Hess & Unger	1917	Clin. ...	60	Unimportant	Common	10 % at 6 mth.
New Orleans	+ +	De Buys ...	1924	Clin. ...	54	Constant	84 %	60 % at 4 mth.
Vienna ...	+ +	Chick et al.	1919	Clin. & X-ray	50+	Sl. enlargemt diagnostic	—	33 % at 6 mth.
Cairo ...	+ + +	Shawki ...	1920	Clin. ...	45	—	—	—

The most prominent clinical signs in the radiographically healed groups were delay in dentition, Harrison's sulcus, pot-belly and slight to moderate degrees of costo-chondral enlargement and ligamentous laxity. Marked beading occurred in 8, and marked looseness of the knees in only 5 cases of this group.

Symptoms of irritability and restlessness were found in one active case and in four healed cases. The unreliability of this feature has already been discussed. Three of the eighteen infants in the whole series to show these symptoms were radiographically negative and were possibly early cases.

The following is quoted as an example of the clinical findings in a patient showing well-marked florid rickets in the X-ray.

Case 56. E. C., female, æt 7 months. One other child in family, father out of work. Fed on dried milk from birth, no cod-liver oil. No previous illness or irritability. Slight nocturnal sweating of head. Sits up quite well. No teeth or signs of same. Head squarish with fontanelle 1½ inches across and parietal bossing. Abdomen negative, knee ligaments moderately lax, and marked costo-chondral beading.

As regards age, all the X-ray positive patients were between 6 and 14 months; and half the clinically positive cases were over this age.

There are many anomalies, however, which are characteristic of the disease and an examination of the radiogram in individual patients frequently produces a surprise. Thus the clinical diagnosis was unsupported by the radiogram in 31 out of 129 cases. Even if one discounts Still's[5] assertion that a negative radiogram does not exclude rickets, and the probability that some of these cases were too early for bone changes to be seen, the radiogram affords a useful check and commentary on purely clinical findings.

Dietetic factors.—From considerations of diet and social conditions alone a vitamin D deficiency was anticipated in 94 or nearly one-half of the whole series of 218 children, which corresponds fairly closely with the clinical results.

Breast-feeding. Statistics and clinical experience are in accord that breast feeding is not necessarily a protection against the development of rickets. Thus Hess and Unger[6] found that one-half of the breast-fed negro population of New York in 1917 showed rickets, though this has since decreased. Aidin[2] states that rickets may occur in the breast-fed as early as the sixth week of life or may be delayed until after the period of breast-feeding is over, even up to four years. There is no doubt, as stated by Pearson and Wyllie, that rickets in the breast-fed provides a high proportion of cases of mild degree. In Manchester, of children weaned before two months, 75 per cent. developed rickets as compared with a general incidence of 26 per cent. in a series of 75 children (Chisholm[7]).

In the present investigation 48 per cent. of the whole number were breast-fed for at least three months immediately prior to the examination. These included over a third of the radiologically active cases, and half the healed cases. Of the 116 clinically positive cases, 43 had been fed at the breast as above described, in 22 instances for a period exceeding 12 months. From an inquiry into the mother's diet and the social condition of the family a deficiency in the vitamin-D content of her food seemed apparent in 41 of 96 nursing mothers. It is to be doubted whether this diet, which was frequently largely composed of vegetables, would be lacking in calcium or phosphorus. Mellanby's[8] work, however, suggests that a vitamin-D deficiency of the mother's diet during pregnancy also, may predispose to rickets in the offspring, a tendency which may not be dispelled by a period of satisfactory diet, and this was probably so in this case. He further holds that a shortage of vitamin A or B facilitates the development of bronchitis

and broncho-pneumonia. The frequency of the former infection among these children at dentition suggests that their diets were further deficient in this factor also.

DRIED MILKS. This diet was exclusive to 39 per cent. of the series, with or without the addition of cod-liver oil, and half the radiologically active cases are in this group. Lactogen was the usual milk taken. Forty-seven of this group were radiographed with 21 positive results. These children formed the majority of the heavy-weight class.

Cases complementarily fed with breast or cow's milk are not considered under this section.

FRESH COW'S MILK. Only 15 of 75 cases receiving adequate amounts of cow's milk showed radiographic evidence of rickets, ten of which were healed; and 21 showed clinical rickets within the present definitions. The contrast between these figures and those for other diets is referred to below.

Anti-rachitic factors.—COD-LIVER OIL. Sixty-seven of the complete series received cod-liver oil for three months or more preceding the day of examination, in some cases (according to the mother) since birth. Thirty of these cases showed clinical, and twenty-six radiographic, signs of rickets. Two reasons may explain these figures. First, it was usually administered in the form of an emulsion containing only approximately 50 per cent. cod-liver oil of B.P. strength, in doses of one drachm thrice daily; and secondly, the necessity for regular administration is neither impressed on nor appreciated by the working-class mother. Some such explanation is necessary since the specific effect of adequate doses of cod-liver oil is beyond all doubt. There is no danger of over-dosage, only of under-dosage, and under its influence the radiogram should begin to show signs of cure in three weeks.

FRESH COW'S MILK. The figures quoted above indicate that, as far as this series is concerned, fresh cow's milk had a greater protective effect than cod-liver oil.

The numbers, and information from the mother only, do not allow of dogmatism, but the contrast is sufficiently marked to be arresting. The vitamin A and D content of cow's milk in Sydney, which mostly comes from animals fed on constantly sunlit pastures, is probably considerably higher than that in most other cities of the world.

SUNSHINE. It is impossible to form a true estimate of the amount of direct sun rays to which these children have been exposed. This point is discussed in the following paragraph.

Discussion.

Sydney is supplied on an average with over 2,000 hours of sunshine annually and the presence of frank rickets to any material degree has been frequently denied by many practitioners of experience. Cases of well-marked natiform cranium or bone deformity have occurred sporadically and have

earned the soft impeachment, but the total number of children with this diagnosis admitted to the Royal Alexandra Hospital for Children during the seven year period 1922-1928 was 51, or approximately 1 in every 1,000 admissions. All were marked to severe cases. Many others, however, are included under diagnoses constituting the catarrhal disorders. Bones X-rayed for other reasons frequently show unequivocal signs of rickets.

Further, osteotomy is not a common surgical procedure at this institution. Harvey Sutton[9] stated in 1920 that 25 per cent. of more than 500 school children in an industrial suburb of Sydney showed slight but definite signs of rickets. This probably refers to evidences of past rickets, but may include some examples of late or continued rickets, as knock-knee of a moderate degree is relatively common in this city, accompanied by considerable sclerosis of the epiphyseal line in the radiogram. The same observer found that in a series of 26 children, 38·7 per cent. of the artificially fed showed clinical rickets as opposed to 10 per cent. among the breast-fed of the series. Craniotabes was noted as being rare. These seem to be the only previous statistics available for Sydney.

Abundantly supplied with sunshine and surf beaches, it is difficult to believe that a deficiency in ultra-violet rays could ever be a factor in the production of rickets in Sydney. With regard to the present series however, it must be remembered that the rickets in the first place is of a mild order, and in the second that only a few could walk sufficiently well to play out of doors in the streets and parks, exposed to the direct rays of the sun. They were usually over-dressed and well covered when taken out of doors, following their first attack of bronchitis or coryza, and spent most of their time in a sole room of a tenement house in a narrow street. No amount of dispersed sunlight or that which has passed through ordinary glass contains many therapeutic rays. Thus Shawki[10] found that 45 per cent. of 500 breast-fed Egyptian children, exposed daily to the bright rays of the Cairo sun, yet swathed in many clothes, showed bony evidences of rickets, and 23 per cent. of apparently healthy infants showed radiological changes. The working-class mother has so far not realized the importance of an adequate daily exposure of her partly undressed child to the direct rays of the sun, which is one of the good teachings of the baby clinics.

Prophylaxis.—The following measures, which are practicable in varying degrees, would help to reduce the ill-results of vitamin-D deficiencies among the children of the poor in Sydney.

1. Public education in the dangers to the child of an ill-balanced diet in the mother as regards vitamin content, during pregnancy and lactation. This could be partly done through the agency of the ante-natal clinics.

2. A stronger insistence on a daily exposure of the half-naked child to the direct rays of the morning sun.

3. The routine provision to all out-patients of a stronger preparation of cod-liver oil in larger doses, and continual instruction of the mother of the need for regular administration.

4. For cases with established rickets, the administration forthwith of irradiated ergosterol which should be made available locally at a suitable price. A portable X-ray machine in the out-patient department should be used for exact diagnosis and control of treatment. A mercury-vapour lamp in a small annexe of the out-patient waiting room would satisfy the physician that he would not have to rely solely on the mother's disposition towards the virtues of natural sunlight. It could also be used continuously for short exposures to waiting infants, as a preventive measure.

5. All dried milk supplied to such infants could be already irradiated. Better still, scalded fresh milk should be supplied and encouraged as the best substitute for human milk in normal infants.

Conclusion.—In reviewing the results reported here it must be remembered that these infants do not represent the child population of the city as a whole. They are selected in so far as they were for various reasons already hospital out-patients. They were nurtured in poor homes during times of industrial distress and this enquiry was conducted towards the end of a rather cloudy winter. The better supervision of diet and conduct exercised on the majority of infants in better class suburbs by means of the baby clinics would undoubtedly bring the general incidence of rickets to a much lower figure, yet ' rickets is probably more often over-looked than any other common disorder of childhood. The number of cases undiagnosed is greater than that of those diagnosed ' (Hess).

Summary.

1. In a series of 218 out-patient children of Sydney between the ages of six months and two years, examined for signs of rickets, sufficient clinical evidence, according to a specified standard, for a diagnosis of past or present disease was found in 52 per cent., the higher incidence falling between the ages of nine to twelve months.

2. Of these children 129 were examined radiologically. Signs of active rickets were found in 12·4 per cent., and of healed rickets in 31 per cent. With 7 doubtful cases, the whole radiographic incidence amounted to 50 per cent.

3. On the whole the infants were well nourished and the disorder of a mild to moderate degree and of an occult character. Correlation between the clinical and radiographic findings showed that marked rib beading and ligamentous laxity with abdominal and hepatic enlargement were the most frequent clinical signs in a small series of radiologically active patients. Symptoms of irritability and spasmophilia were rare; craniotabes and epiphyseal enlargement were notably absent. Apparently only a cautious reliance should be placed on alterations in size of the fontanelle and delay in teething or walking. Dentitional bronchitis is very common.

4. Examination of the diets of these children showed that on theoretical grounds evidences of vitamin A and D deficiency could be anticipated in

43 per cent. In 41 of 96 nursing mother's diet was deemed unsatisfactory from this standpoint. Breast-fed infants provided over a third of the radiologically active and a half of the healed cases of rickets.

5. Fresh Sydney milk which is mostly from the country seems to have a good protective effect, better at least than insufficient amounts of cod-liver oil.

6. The cause of this high incidence among the hospital class is possibly partly attributable to insufficient ultra-violet irradiation, which should correct a dietetic vitamin shortage.

7. Certain suggestions are made towards prophylaxis mainly based on the principle of making positively sure that each infant receives an adequate daily amount of direct sunlight or of ingested vitamin D.

I express my sincere gratitude to Dr. Robert Dick, Jnr., for taking the radiograms; to the Gloria Light Co. for the supply of films and a transformer; and to the Out-Patient Staff of the Renwick Hospital for allowing me to see their cases.

REFERENCES.

1. De Buys, L. R., *Am. J. Dis. Child.*, Chic., 1924, XXVII, 149; 1926, XXXI, 727.
2. Aidin, R., *Arch. Dis. Childh.*, Lond., 1927, II, 155.
3. Hess, A. F., *Abt's Pediatrics*, Philad., 1926, II, 908.
4. Pearson, W. J., & Wyllie, W. G., *Rec. Adv. Dis. Child.*, Lond., 1928, 135.
5. Still, G. F., *Common Disorders of Childh.*, Lond., 1926, 82.
6. Hess, A. F., and Unger, L. F., *Abt's Pediatrics*, Philad., 1926, II, 912.
7. Chisholm, C., *Brit. Med. J.*, Lond., 1926, i, 741.
8. Mellanby, E., *Loc. cit.*, 515.
9. Sutton, H., *Med. J. Austral.*, Sydney, 1920, ii, 190.
10. Shawki, I., *Lancet*, Lond., 1930, i, 974.

CONGENITAL OBSTRUCTION OF THE FEMALE URETHRA

BY

OSWALD ADDISON, F.R.C.S.

(From the Hospital for Sick Children, Great Ormond Street, London.)

Congenital obstruction of the male urethra by a diaphragm, or more frequently by valves of mucous membrane in connection with the veru-montanum, has been recorded from time to time, and in recent years an increasing amount of attention has been given to this condition.

In the female any kind of congenital obstruction of the urethra appears to be extremely rare, and I have been able to find so few references to it, that the following case seems worth putting on record.

O. W., female, aged 4 years, was admitted to the Hospital for Sick Children, Great Ormond Street, under Dr. Hutchison, on Oct. 4th, 1930. She had been ill for three weeks, vomiting after every meal. She had never been strong, having been undeveloped since birth. 'Always troubled with her water, never seemed to make water like anyone else, only in dribbles. She always used to strain; nearly always a motion as well.' She had suffered from prolapse of the bowel at 3 years from straining.

On admission she appeared a thin, poorly developed child, yellow, lethargic and looking very ill. The bladder was very hard and prominent above the pubes. The child was unable to empty the bladder and had to be catheterized daily, purulent urine being drawn off. The urine showed a thick deposit of pus and gave a profuse growth of streptococci. After being emptied by catheter, the bladder could still be felt as a hard supra-pubic mass. Blood urea 394 mgrm. per 100 c.cm.

The child's condition did not improve, she became more drowsy, and vomited frequently. A cystogram (sodium iodide, 13 per cent.) was taken on Oct. 16th, and showed a small bladder not quite filling the pelvis. The ureters were greatly enlarged and convoluted. Immediately behind the symphysis and continuous with the floor of the bladder was a cavity filled with the iodide solution. This cavity was about three-quarters of an inch in diameter and showed a rounded lower border. It was considered to be the dilated proximal part of the urethra, and this was subsequently found to be the case.

A cystoscopic examination was made, but owing to the impossibility of obtaining a clear medium, it was unsatisfactory. On passing an instrument a slight resistance was felt about half an inch from the external meatus. The urethra was dilated and a catheter was tied in.

Patient gradually became more drowsy. The blood urea rose to 427 mgrm. per 100 c.cm. three days before death on October 23rd.

POST-MORTEM EXAMINATION.—The kidneys were enlarged and dripped pus on section. The pelves were thickened and dilated. The calices were dilated and a number of subcortical abscesses were present in each kidney. The capsule was thickened and very adherent; the kidney substance was pale and sclerosed. The ureters were both greatly dilated but not tortuous. The bladder was much thickened and moderately dilated.

A large probe was passed easily through the urethra from the bladder. The bladder was then carefully opened up from above downwards. In the middle of the urethra was found a tag of mucous membrane folded on itself and forming an

oval projection about one-eighth of an inch long on the posterior wall on the left side. There were two small areas of damaged epithelium either of which might have been points of attachment for the free end of the tag.

Discussion.

I think the tag of mucous membrane was almost certainly the remains of a valve or diaphragm that was ruptured when the urethra was dilated and a catheter tied in. The stretching of the urethra and tying in a catheter also

FIG. 1.—Cystogram, sodium iodide 13 per cent. Bladder of moderate size, outline slightly irregular at sides. Behind the symphysis, continuous with the base of the bladder is a hemispherical swelling due to the dilatation of the urethra. The ureters are both greatly distended and somewhat convoluted.

probably accounted for the fact that the dilatation of the urethra proximal to the tag was not nearly so great as was expected from the cystogram.

Congenital valvular obstruction of the male urethra has been recorded many times since Langenbeck[1] first published an account of the condition, but it was not recognized clinically until 1913 when Professor Young[2] of Johns Hopkins Hospital published the first case diagnosed, and successfully operated upon. In 1919 with Frontz and Baldwin[3] he published further cases, and in 1929 with McKay[4] he recorded a total of twenty-one cases with fifteen successful operations. Recently Campbell[5] has recorded eighteen

more cases. In this country records of cases have been published by Poynton and Sheldon[6], King and Sheldon[7] and by Addison[8].

Nunez[9] records two instances in new-born girls, where the urethra was obstructed by a diaphragm at or just within the external meatus. In one the obstruction was complete. He also reports another case, born dead, with imperforation of the anus and urethra, the latter being elongated and prolapsed for three centimetres below the pubic arch forming a transparent

FIG. 2.—Bladder and urethra opened from the front. The enlargement of the ureters and very great hypertrophy of the bladder show well, but the fold of mucous membrane in the urethra, indicated by the rod, does not stand out very clearly.

cylindrical tube. Rocher and Marc Riviere[10] report a case of obstruction by diaphragm at the meatus in a new-born girl.

Nové-Josserand and Gayet[11] in an article on malformations of the urethra mention similar cases, including three recorded in adult life, in one of which the urethra behind the stricture was as large as a mandarin orange. They were readily cured by dilatation; no satisfactory explanation of the method of development of the malformation is given. They also quote the following:—

Enfin Barthélémy Cabrol avait déjà publié en 1552 un récit d'une delicieuse naïveté, mais d'une observation très precise, concernant une jeune fille de la ville Beaucaire. 'Et trouvay son ombilic allongé de quatre doigts et semblable à la

creste d'un coq d'Inde, et qu'elle pissait constamment par l'ombilic tout ainsi qu'elle faisait dans la ventre de sa mère, l'orifice de la vessie fermé d'une membrane épaisse d'un teston au plus, le reste bien formé, et ayant fait l'ouverture, lui mit une canule de plomb jusqu'en dedans du corps de la vessie pour tenir le conduit libre.' Symptômes et traitement, tous est déjà contenue dans cette vieille observation.

FIG. 3. Enlarged view of bladder and urethra opened from the front. The rod points to the fold of mucous membrane on the posterior wall of the urethra.

REFERENCES.

1. Lagenbeck, *Mem. sur la lithotomie*, 1802.
2. Young, H., *Johns Hopkins Medical Society*, 1913.
3. Young, H., Frontz, W. A., & Baldwin, J. C., *J. Urology*, Balt., 1919, III, 289.
4. Young, H., & McKay, R. W., *Surg. Gynec. Obst.*, Chic., 1929, XLVIII, 509.
5. Campbell, E., *J. Am. Med. Ass.*, Chicago, 1931, XCVI, 592.
6. Poynton, F. J., & Sheldon, W., *Arch. Dis. Childh.*, Lond., 1927, II, 252.
7. King, H. B., & Sheldon, W., *Lancet*, London, 1928, ii, 1126.
8. Addison, O., *Arch. Dis. Childh.*, Lond., 1929, IV, 255.
9. Nunez, J. E., *Thèse Paris*, Paris, 1882.
10. Rocher, H. L., & Reviere, M., *Bull. Soc. Obst. et Gyn.*, Paris, 1927, XVI, 325.
11. Nové-Josserand, G., & Gayet, G., *Encyc. franc. d'urol.*, Paris, 1922, V, 852.

LYMPHOCYTIC LEUKÆMIA CAUSING PONTINE HÆMORRHAGE

BY

J. C. HAWKSLEY, M.D., M.R.C.P.
(From the Children's Hospital, Birmingham.)

The symptoms and signs associated with lymphocytic leukæmia are numerous, and depend principally upon five factors which may be thus summarized:—

1. Changes in the circulating blood.
2. Pressure from enlargement of lymphoid structures, or from deposits and infiltrations of lymphoid cells.
3. Infiltrations of various organs interfering with their functions.
4. Hæmorrhage, which may be due to blood changes, weakening or infiltration of the vessel walls.
5. Metabolic disturbances not covered by the factors mentioned already, such as pyrexia, and due probably or possibly to the poisonous effects of the disease itself. Such pyrexia will occur with new growths, such as carcinoma and sarcoma, as well as in leukæmias.

Considering the relative commonness of leukæmia and the extensive literature upon it, it is none the less apparent that involvement of the nervous system is amongst its rarer manifestations. It is for this reason, and also because of the typical syndrome which was produced, that the following case is recorded.

Case report.

B.S., a girl of ten and a half years, was sent by her doctor to the Birmingham Children's Hospital with the history that she had been limping slightly for three days, and on the night before being sent up to hospital, had suddenly become paralysed all down the left side. For three weeks previous to this she had been languid, and for a fortnight had been coughing and expectorating frothy sputum. A fortnight before admission she had developed bilateral subconjunctival hæmorrhages, for which she attended an eye hospital, where the condition was attributed to coughing.

On admission she was conscious, rational and spoke clearly. She was well-nourished and rather pale: there were hæmorrhages under both conjunctivæ and bruising of both upper eyelids. There were slight cough and some dyspnœa, but no stridor.

Physical examination revealed a general enlargement of the glands in both axillæ, both groins and in the neck. Her spleen was enlarged down to the pelvis and her liver almost to the umbilicus. No ascites was present.

There was a large pleural effusion on the left side, sub-manubrial dullness was absolute, and the sign known as paravertebral tracheophony was present as far down as the fifth dorsal vertebra on both sides.

Examination of the central nervous system revealed a left hemiplegia in which the face, tongue and masticatory muscles of the same side shared.

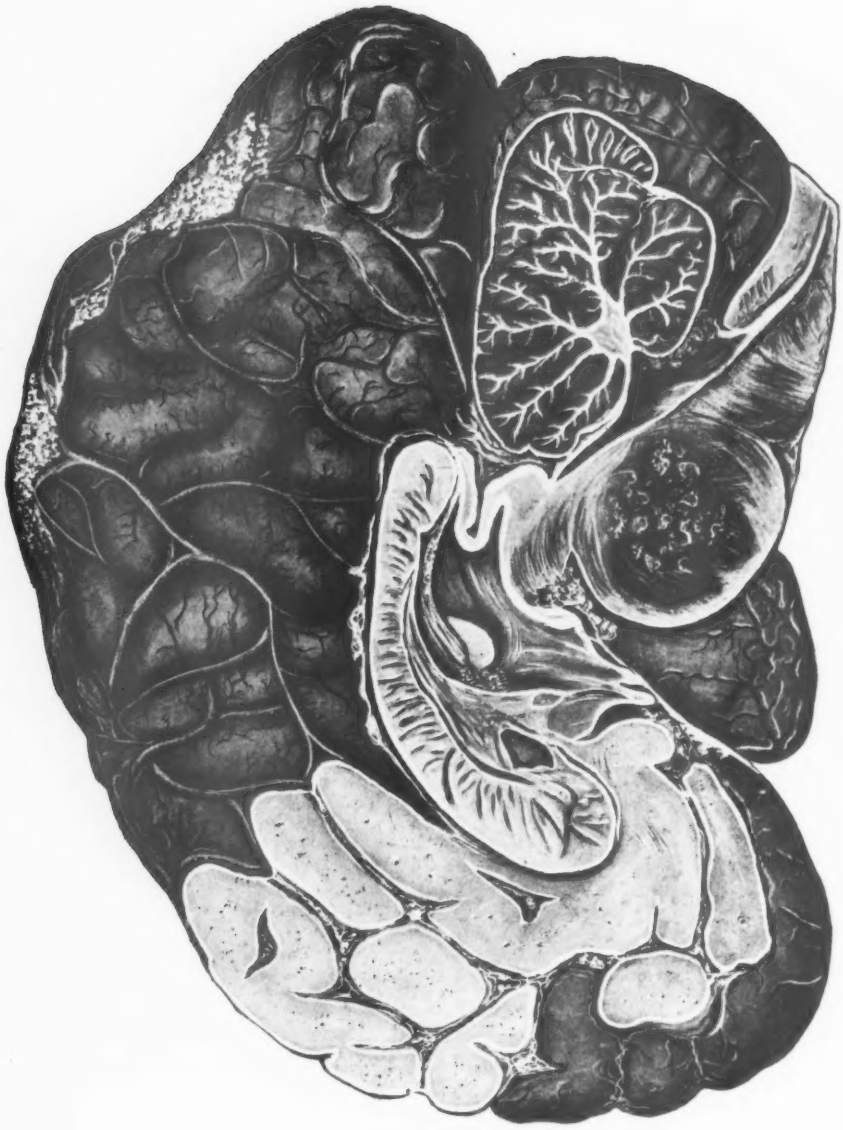

FIG. 1.—Brain after sagittal section showing haemorrhage into the pons Varollii.

The eye movements were normal, both pupils reacted to light and were central and circular, the right one being a trifle more dilated than the left. The fundi were pale, but showed no pathological change.

The diagnosis was made of lymphocytic leukæmia, complicated by a left pleural effusion, and intra-cranial hæmorrhage. The fact that the whole of the left side was paralysed made it probable that the lesion lay at a point where the pyramidal tract could be injured en masse in a small area such as the internal capsule or pons. As large a cortical hæmorrhage as would have been needed to paralyse an entire side would certainly have caused other and severe manifestations.

A complete blood count was unfortunately not done at the time, and was thus lost as she died next day. A smear taken on admission showed a marked white-cell increase, about 90 per cent. of the white cells being lymphocytes.

For twelve hours there was no change, then she quite rapidly became comatose. Her temperature rose to 106°, and she developed pin-point pupils. The location of her hæmorrhage was now no longer in doubt. She died a few hours later.

Fig. 2.—Pons under low power showing infiltration.

Autopsy. At autopsy there was found marked enlargement of all the lymph glands. The mediastinum was one mass of growth in which the aorta, trachea and œsophagus were buried. There was a large amount of fluid in the pericardium and a large effusion into the left pleural cavity.

The spleen was greatly enlarged, soft and to the naked eye appeared homogenous; the liver was large and pale, having many small whitish areas scattered about its cut surface.

On examining the contents of the skull there was no sub-arachnoid hæmorrhage and no gross change in the cerebrum or cerebellum. The pons was bulging on both sides and section revealed a large hæmorrhage involving chiefly the right side, but in part also the left. Fig. 1 shows the appearance on hemisection of the brain.

Microscopical examination of the liver showed periportal lymphocytic infiltration. There was well-marked infiltration of the spleen, kidneys and mediastinal structures. Microscopy of the pons showed it to be heavily infiltrated all round the area of hæmorrhage with lymphocytes; the appearance is shown in the microphotographs (Figs. 2 and 3).

Sections taken from the various areas of the cerebrum and cerebellum showed no abnormality.

Discussion.

The nervous manifestations of leukæmia have been classified by Tapie and Cassar[1], who in recording a case of hæmorrhage due to leukæmic infiltration of the internal capsule describe the following varieties:—

1. Medullary degeneration: small foci of sclerosis or capillary hæmorrhage in the brain or cord.
2. Leukæmic infiltration: this may or may not cause symptoms.
3. Hæmorrhages into nerve centres.
4. Nerve lesions due to compression.
5. Zoster.

The case here described will, under this classification, come into both the second and third types, being due to hæmorrhage, itself probably caused by the leukæmic infiltration.

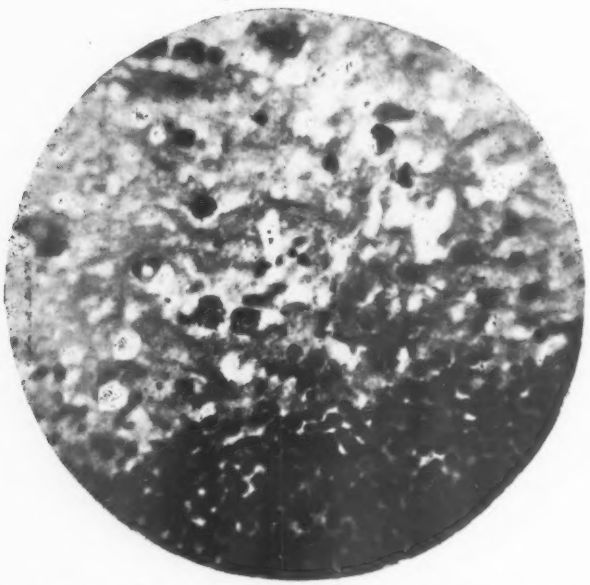

FIG. 3.—Pons under high power showing infiltration.

The child had, as before mentioned, been limping for three days previously to the onset of hemiplegia. Whether the initial limping was due to the infiltration alone, or to a small and earlier effusion of blood it is impossible to say; Tapie and Cassar themselves say that the infiltration may or may not cause symptoms. It seems, however, more probable that the infiltration alone was responsible, as in such an area a hæmorrhage would have to be very small, and occur very gradually not to cause some sudden change in the reactions of the central nervous system. The sequence of events which seems to explain the symptoms is as follows: first, a gradual infiltration of the pons, eventually causing slight involvement and resulting in a limp; then a hæmorrhage, which resulted in a sudden hemiplegia; finally an increase in the hæmorrhage causing coma, the pontine syndrome and death.

The relative rarity of nervous complications in the leukæmias of childhood has already been mentioned. Ramsay[2], in an analysis of a hundred cases of leukæmia in children under eight years of age, does not mention one in which the nervous system (apart from the fundus oculi) was involved. He states that ' The patient may die with hyperpyrexia suggesting some toxic action on, or a leukæmic infiltration of, the pons Varollii.' He does not, however, describe or quote an actual case.

Munro[3] describes a case of a female in the twenties, whose symptoms and signs suggested meningitis, and whose cerebro-spinal fluid was blood-stained and under increased pressure. Post-mortem examination revealed the fact that she had myeloid leukæmia. The vessels of the meninges showed marked engorgement, and there was acute œdema of the brain and cord. No gross hæmorrhage was found.

The case described here was not investigated by lumbar puncture, but autopsy revealed no hæmorrhage into the meninges.

Bass[1], in a review of the cases of leukæmia in children at the Mount Sinai Hospital from 1911-1921, found four to have shown involvement of the brain. The first, which soon died, had hepatic and splenic enlargement, and signs of meningeal irritation. Post-mortem examination revealed a large hæmorrhage over the surface of the brain and the usual systemic appearances of leukæmia. The second, third, and fourth cases all died with convulsions, delirium and coma; these are not so fully described as the first case.

He quotes another case, in which he performed a necropsy and found large, brick-red masses, up to the size of a cherry, involving the brain; these proved to be leukæmic deposits. There had been no nervous disturbances until a few days before death. He states that leukæmic infiltration of the brain may affect considerable areas before causing symptoms.

He quotes Munro's case, already mentioned, and states that he has seen altogether six cases with symptoms referable to the central nervous system. Of these, four were examples of cerebral hæmorrhage. Three of these were verified post mortem; two had also been lumbar punctured; and the last had been diagnosed clinically but was not verified after death.

The case recorded here in no way resembled any of these clinically, and post-mortem examination revealed what macroscopically appeared to be simply a pontine hæmorrhage.

Allbutt and Rolleston[5] record a case of leukæmia with multiple cerebral and cerebellar hæmorrhages. They conclude that the hæmorrhages were probably due to badly nourished vessels becoming thrombosed, the condition most likely beginning in the small veins.

The case that has been described agrees with the statement of Tapie and Cassar that infiltrations may or may not cause symptoms; this having caused none until four days before death. It also provides an example of the termination of life with hyperpyrexia mentioned by Ramsay.

Summary.

A case of hæmorrhage following leukæmic infiltration of the pons Varollii is recorded and compared with other examples of disease of the central nervous system due to leukæmia.

I am grateful to Dr. L. G. Parsons, who has allowed me to record the notes of this case which was under his care. I wish also to thank Dr. Gittins, pathologist to the Children's Hospital, Birmingham, for his help with the microscopy, and Mr. Brain, medical artist, for the illustration and micro-photographs.

REFERENCES.

1. Tapie, J., & Cassar, A., *Arch. de mal. du coeur.*, Paris, 1919, XII, 218.
2. Ramsay, G. W. St. C., *Arch. Dis. Childh.*, Lond., 1927, II, 119.
3. Bass, M. H., *Am. J. Med. Sci.*, Philad., 1921, CLXII, 647.
4. Munro, E. E. H., *J. Am. Med. Ass.*, Chic., 1920, LXXIV, 603.
5. Allbut, C., & Rolleston, H. D., *System of Medicine*, Lond., 1909, Ed. 2nd, V, 802.

TUMOUR OF THE SUPRARENAL CORTEX IN AN INFANT OF 18 WEEKS

BY

REGINALD LIGHTWOOD, M.D., M.R.C.P., D.P.H.
(From the Hospital for Sick Children, Great Ormond Street, London.)

The functional importance of the suprarenal medulla was recognized for some years before that of the cortex was fully appreciated. While animals can live perfectly well without the medullary portion, total adrenalectomy causes death. From this and other data it is known that the cortex produces one or more hormones indispensable to life, and it would appear that the cortex is by far the more important element. The part played by these cortical hormones in the growth and maintenance of the genital system and of the secondary sexual characters has been a fertile field of study in which distinction has been won by physicians, pathologists, anatomists and physiologists alike.

As early as 1806, F. Meckel[1], from studies in comparative anatomy, developed the idea of a relationship between the suprarenals and the sexual organs, his belief being that animals with prepotent sexual powers had large suprarenals. It does not appear that he recognized the separate importance of the suprarenal cortex. In 1816 Otto[2] reported hypertrophy of the genital organs associated with hypertrophy of the adrenal. In 1905, there appeared a classical paper by W. Bulloch and J. H. Sequeira[3], who described a case of a neoplasm of the suprarenal cortex in a female of eleven years, manifesting hirsuties with precocious growth and menstruation. Their suspicion that the simultaneous occurrence of the suprarenal tumour with precocity was no matter of chance was confirmed by a study of the literature. Going back to 1756 they were able to review twelve cases (all in children), and to originate the idea that hyper-function of the suprarenal cortex was the cause of the precocity in such cases. Though Bulloch and Sequeira pointed out that there are certain tumours of the suprarenal in young children not associated with evidence of precocious development, they did not recognize that these involved essentially the medullary portion. The work of R. Hutchison[4], R. S. Frew[5] and others has placed these cases in an entirely separate group, now known by such names as medullary hypernephroma, sympathetic neuroblastoma and neurocytoma sympatheticum. Among the effects of tumours of the cortex Bulloch and Sequeira gave excessive growth, hirsuties, precocious puberty, adiposity and muscular over-development. The youngest of their cases was 14 months old, and the oldest 14 years old. The average age of their series was 5 years, and only two were observed after the age of 7. This paper, which moulded physiological opinion regarding cortical function, has been followed by several notable contributions. In 1912, E. Glynn[6] was able to add five more cases to the twelve already collected by Bulloch and

Sequeira. He employed the term adrenal hypernephroma in his description, and tabulated the features of the seventeen cases to show that such hypernephromata are commoner in females and tend in them to increase the male primary and secondary sex characters at the expense of female characters. Further, he gave six examples of adrenal hypernephroma in young adult females associated with changes in sex characters, and he broke new ground by giving thirteen examples of the association of pseudo-hermaphroditism with bilateral hyperplasia of the adrenal glands, or of adrenal rests. His conclusions are of much interest:—

> These cases . . . . . may be roughly divided into two groups:—
>
> Group 1. The adrenal enlargement is unilateral, microscopically neoplastic; it often produces metastases and directly, or indirectly, causes death; but growth takes place more slowly than most malignant tumours. The growth and its associated physiological and anatomical defects are most probably acquired.
>
> Group 2. The adrenal enlargement is bilateral, microscopically hyperplastic. Metastases are absent, though rests may occur, and death is due to other causes. The adrenal lesions and their associated physiological and anatomical defects are most probably congenital.
>
> The line of demarcation between those two groups, however, is not complete, for some of the cases are intermediate.

G. Holmes[7] (1925) in a paper recording a case of virilism associated with suprarenal tumour in a female was able to show that complete recovery from the structural, functional and psychological changes occurring in virilism, could follow surgical removal of a tumour of the suprarenal cortex. He remarks that ' the disappearance of the virilism after operation is evidence as strong as we can hope to obtain from clinical sources of the causal relation in which the tumour stood to it.' Several other examples of successful surgical removal with disappearance of virilism have been recorded.

R. Hutchison[8] has reported the interesting association of hemi-hypertrophy (hemi-macrosomia) with hypertrophy of the suprarenal on the same side, but it would appear that the suprarenal enlargement may have been a part of the process rather than its cause.

Though generally speaking it is correct to say that tumours and hyperplasias of the suprarenal cortex produce virilism, the exact nature of the clinical types produced depends on several factors, namely, on sex and age, and on the duration, rapidity and extent of the growth. The influence of sex and age has been worked out by Glynn and illustrated by tabulations of the features of the collected cases.

In children, the cases have been divided by L. Guthrie and W. Emery[9] into two types*:—(1) The ' infant Hercules ' or muscular type. This occurs only in males. True sexual precocity may appear. (2) The obese type with hirsuties. This occurs in both sexes. Of these, the infant Hercules type is the better known, perhaps on account of its happy title; nevertheless, it is less common than is the obese type for the infant Hercules appears only in some of the male cases, whereas tumours of the suprarenal are commoner in females.

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* This division was originally suggested by Dr. F. Parkes Weber.

A good example of the infant Hercules clinical type is a case described by C. E. Adams[10] as follows:—

Considering his age he presented remarkable appearances of precocious development. As a child nothing unusual had been observed, but puberty set in at the age of 10 years, from which time, although he increased little in height, he developed great muscular strength, excelled in athletic sports, and defeated all competitors. For two years his complexion had been observed to be plethoric and dusky, and during this period the growth of hair on his face had to be shaved almost daily. His general appearance was that of a sturdy little man. This boy died of a malignant growth of the left suprarenal cortex.

The obese type of suprarenal virilism manifests itself in adiposity and hypertrichosis, with or without precocious puberty. Guthrie and Emery's description of this type in children may be quoted:—

In precocious obesity the features are bloated, the cheeks swell with fatness, the complexion is dusky and congested. The fat is usually distributed evenly about the body, but the extremities may remain thin. Pads of fat are situated about the neck, breasts, and flanks; a lipomatous mass is sometimes seen between the shoulders.

Guthrie's case occurred in a boy; an illustration of this child at $4\frac{3}{4}$ years can be seen in ' Diseases of Children ' (second edition), edited by H. Thursfield and D. Paterson.

The youngest recorded instance of a cortical tumour is that of A. Collett[11].

This was a female child in whom a growth of pubic hair was noticed between 6 and 8 months. This gradually became thicker, and spread to the limbs and trunk. She became fat and heavy, growing excessively. The voice became deep and rough. At 18 months she was above average length and weight, her head was large and her cheeks bulged. There was hair on the labia, mons Veneris, thighs, shoulders, and back. There was over-development of the clitoris, which became a penis-like organ with glands, corona, and prepuce, and on its under surface a urethral groove was to be seen. A left suprarenal tumour was removed when she was 2 years and 2 months old. Within two months of operation there was already striking improvement, the cheeks became smaller, she became more child-like in appearance, but even two years after operation she was not a normal child.

In Collett's case we have an excellent example of Guthrie's obese type in a female infant with hirsuties, and virilism amounting to pseudo-hermaphroditism.

A. D. Fordyce and W. H. Evans[20] have recorded two cases of cortical hypernephroma, the first a male of $2\frac{1}{4}$ who died after an operation for the removal of the tumour, the second a female of 2 years who in many respects resembled the infant described by Collett; recovery followed extirpation of the growth.

Case report.

Even younger than Collett's is the following case of a male infant in whom symptoms arose at eleven weeks, which brought him under observation at the age of eighteen weeks. This case was briefly presented before the British Pædiatric Association in 1931 by R. Hutchison and the writer[12]. The full details are now recorded for the first time.

A male infant, a fourth pregnancy, and one of twins, made good progress until the age of 11 weeks. Then the mother became aware that there was enlargement of his cheeks and chin. Subsequently she found diffuse swelling at the back of his neck and between the shoulder blades. The legs began to waste, advance in weight

slowed down, and finally he began to lose. He ceased to take any interest in his surroundings, and thrush appeared. At the age of 18 weeks he was admitted to the Hospital for Sick Children under the care of Dr. Robert Hutchison.

The parents were healthy, and all their six children were alive. No serious illnesses had occurred among them, except tuberculous adenitis in the eldest. The other twin was thriving.

FIG. 1.—Post-mortem photograph. Note the fat, blotchy cheeks and hairiness of the forehead.

The appearance of the baby (Fig. 1) was very peculiar on account of the visible, hard deposits of fat in the cheeks and around the shoulders and scapulæ. The cheeks had a florid colour bringing to mind the countenance of a bar attendant accustomed to good living. The hair on the head was plentiful, and there was a slight abnormal hairiness of the forehead, but no development of hair elsewhere. The skin was dry and scaly in places, the legs wasted, and genitalia normal. There was no enlargement of lymphatic nodes. In the left flank was a mass which felt larger and lower than a

normal left kidney. The right kidney was palpable and the liver not enlarged. The urine was normal and the Wassermann reaction negative. A tentative diagnosis of left (cortical) suprarenal tumour was made; horseshoe kidney and congenital cystic kidney also being considered in the diagnosis.

After admission the infant's weight fell steadily. In a week the temperature and respiration rate began to rise and signs of pneumonia appeared in the right lung.

FIG. 2.—Adenoma of the suprarenal cortex. The upper pole of the kidney is flattened out by the tumour.

At this time a routine blood count presented the interesting feature of nearly 4,000 normoblasts per c.mm. (28 per 100 white cells counted):—

Red blood cells	4,375,000 per c.mm.
Hæmoglobin	60 per cent.
Colour index	·7
White blood cells	14,000 per c.mm.
Polymorphonuclears	20 per cent.
Lymphocytes	73 ,, ,,
Monocytes	5 ,, ,,
Myelocytes	1 ,, ,,
Lymphoblasts	1 ,, ,,

Poikilocytosis, anisocytosis and polychromasia were noted.

The temperature rose to 103°, diarrhœa and vomiting began, and eleven days after admission the patient died.

AUTOPSY. There was an excess of fat over the thorax, neck and upper part of the back. The legs and arms were wasted in contrast to the plump face and thorax. The fat was firm and had the appearance of beef suet. The sucking pads were large. There was pneumonic consolidation of the right lung. The left ventricle was hypertrophied, its wall being 8 to 10 mm. thick. The kidneys were of average size for this age. The left suprarenal formed a round mass as large as the left kidney to which it was attached (Fig. 2). The tumour was completely encapsuled; no infiltration could be seen, and no metastases. The tumour had displaced the left kidney downwards into the left loin, making it abnormally palpable during life. On section

the suprarenal tumour presented macroscopically a heterogeneous appearance in which areas of hæmorrhage and necrosis could be recognized.

On microscopical examination the main part of the section, stained with hæmatoxylin and eosin, was seen to consist of a mass of cortical cells which formed a cortical adenoma (Fig. 3). In this adenoma there was no trace of the normal arrangement in zones. The cells were arranged, however, in a manner closely similar to the normal: cell-groups and trabeculæ being separated by capillaries and delicate collagen fibrils. Some of the groups were abnormally large, and the cells themselves, though they varied in size, were typical of cortical cells and there was no evidence of malignancy (Fig. 4). On the surface of the tumour was a portion of suprarenal showing a more normal arrangement, except that here was seen a fibrosis of the medulla which contained no glandular tissue, and the cortex, fibrosed in some places, was elsewhere hyperplastic.

Dr. H. M. Turnbull, who kindly examined the tumour, described it as a cortical adenoma (or benign hypernephroma), and Dr. H. A. Lucas, who also kindly gave an opinion, agreed that there were no signs of malignancy.

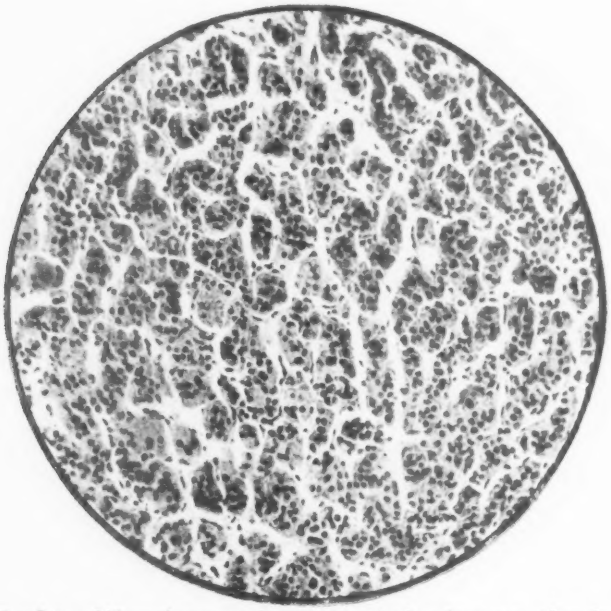

FIG. 3.—Microphotograph of cortical adenoma showing the arrangement of the cells in groups and columns. (Low power × 100).

Ewing[13], in 'Neoplastic Diseases,' points out that the distinction between adenoma and nodular hyperplasia of the adrenal cortex is not a sharp one and that, indeed, it is possible for the two processes to be found side by side in the same gland (Letulle). Malignant transformation in such tumours is of relatively common occurrence.

Discussion.

This case combined slight hypertrichosis with obvious adiposity. Pathologically the neoplasm was unilateral and apparently benign in character, although it is possible that, had the infant survived longer, secondary deposits might have been formed. To fix the date at which the tumour process became active we can be guided by the appearance of macrosomia at eleven weeks, suggesting that the disease was entirely post-natal. It is reasonable to leave it an open question whether a longer course

would have given time for the features of malignancy to manifest themselves, and it should be remembered in this connection that malignant cortical hypernephromata may be expected to metastasize slowly.

The histological appearances in this case were very similar to those seen in the micro-photographs reproduced in Bulloch and Sequeira's paper, and, except for the absence of secondary deposits, the pathological findings must have been very similar. Moreover, the same macroscopical and microscopical similarities crop up again and again in the literature of these tumours.

High blood pressure with cortical tumours has been recorded[14, 15], and the finding of hypertrophy of the left ventricle in the present case, without any cardiovascular or renal explanation, was of great interest. Unfortunately no record of the blood pressure had been secured. In cases of cortical

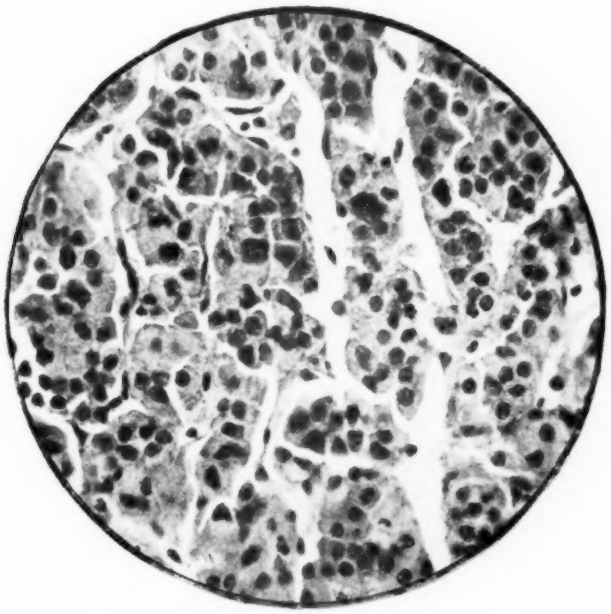

FIG. 4.—Microphotograph of cortical adenoma. The cortical cells vary in size and shape and they are separated by capillary loops. (High power × 250).

tumour with raised blood pressure, an associated functional hyper-activity of the suprarenal medulla has been suggested, and whatever its explanation may be its occasional occurrence must be accepted. Increased vascular supply of the tumour-bearing gland, with increased activity of the medulla, might be put forward in explanation, except that raised blood pressure is the exception rather than the rule in nearly all types of suprarenal tumours, even in the medullary ones themselves. Indeed, it is only in that rare variety, the suprarenal paragangliomata, that high blood pressure is a feature. On the other hand, it may be that cells of the cortex themselves elaborate a pressor hormone and this explanation would fit the facts more satisfactorily.

Recently, our knowledge of the action of a cortical hormone has been increased by the experiments of Hartman, MacArthur, Brownell and Hartman[16] and by those of Swingle and Pfiffner[18]. These two groups of

workers have independently prepared extracts of the adrenal cortex which they have shown to be capable of prolonging indefinitely the lives of adrenalectomized animals. Both the Swingle-Pfiffner extract and the Hartman extract (Cortin)[17] have been tried in the treatment of Addison's disease with striking benefit. Details of seven cases treated with the extract of Swingle and Pfiffner have been recorded[19], though blood pressure readings taken after the treatment are mentioned in but two of them. In the first, the blood pressure before treatment was 80-84 mm. systolic, and 58-60 mm. diastolic. After treatment it was 106 systolic, and 58 diastolic. In the second, the initial reading was 82 systolic and 64 diastolic, and after treatment it was 100 systolic and 75 diastolic. The earlier cases in this series received an extract not quite free from adrenalin, so that observations on them would not have been helpful for our purpose. The Hartman extract revived a patient with a systolic pressure of 50 mm. The Swingle and Pfiffner extract proved effective, as a rule, within 48 to 72 hours. The most striking results were a return of appetite, a sense of well-being and a gain in weight. The rise in blood pressure did not appear to be striking in comparison with the subjective improvement, though perhaps it would be wrong for us to assume that the cortical extracts so far employed have been capable of exerting a full physiological action.

My thanks are due to Dr. Robert Hutchison for permission to publish the details of this case, and to Professor H. M. Turnbull and to Dr. H. A. Lucas for their histological opinions.

REFERENCES

1. Meckel, F., *Abhandlungen aus der Menschlichen und Vergleichenden Anat. und Physiol.*, Halle, 1806, 164. (Quoted by W. Bulloch and J. H. Sequeira.)
2. Otto, *Pathologisch-Anat. Beobachtungen*, 1816, 139. (Quoted by Apert, *Bull. med.*, 1910.)
3. Bulloch, W., & Sequeira, J. H., *Tr. Path. Soc. Lond.*, London, 1905, LVI, 189.
4. Hutchison, R., *Quart. J. Med.*, Oxford, 1907-8, I, 33.
5. Frew, R. S., *Ibid*, 1911, IV, 123.
6. Glynn, E., *Ibid*, 1912, V, 157.
7. Holmes, G., *Ibid*, 1925, XVIII, 143.
8. Hutchison, R., *Brit. J. Child. Dis.*, London, 1904, I, 258.
9. Guthrie, L., & Emery, W. d'E., *Clin. Soc. Trans.*, London, 1907, XL, 175.
10. Adams, C. E., *Tr. Path. Soc. Lond.*, London, 1905, LVI, 208.
11. Collett, A., *Norsk. Mag. f. Laegev.*, Christiania, 1923, XXXIV, 609; and *Am. J. Dis. Child.*, Chicago, 1924, XXVII, 204.
12. Hutchison, R., & Lightwood, R., *Arch. Dis. Childh.*, Lond., 1931, VI, 257.
13. Ewing, J., *Neoplastic Diseases*, Philad., 1928, 3rd Ed., 811.
14. Weber, F. Parkes, *Practitioner*, Lond., 1920, CV, 181.
15. Winkel, M., *Deut. Arch. f. klin. Med.*, Leipzig, 1928, CLIX, 1. (Quoted by F. Parkes Weber.)
16. Hartman, F. A., MacArthur, C. G., & Hartman, W. E., *Proc. Soc. Exper. Biol. and Med.*, N.Y., 1927, XXV, 69.
17. Hartman, F. A., Brownell, K. A., & Hartman, W. E., *Am. J. Physiol.*, Baltimore, 1930, XCV, 670.
18. Swingle, W. W., & Pfiffner, J. J., *Science*, N.Y., 1930, LXXI, 321.
19. Rowntree, L. G., Greene, C. H., Swingle, W. W., & Pfiffner, J. J., *J. Am. Med. Ass.*, Chicago, 1931, XLVI, 231.
20. Fordyce, A. D., & Evans, W. H., *Quart. J. Med.*, Oxford, 1929, XXII, 557.

UMBILICAL DIPHTHERIA

BY

A. GORDON SIGNY, L.R.C.P., M.R.C.S.,
Assistant Pathologist and Research Fellow,

AND

R. DOUGLAS BRUCE, M.B., Ch.B.,
House Surgeon.

(From the Hospital for Sick Children, Great Ormond Street, London.)

This unusual condition was first described in 1878 by Löwenstamm[1] but the first authentic case proven by culture and post-mortem examination occurred in 1896[2]. The only English case was reported by Pitts[3] in 1897, also from this hospital, and in this the umbilical condition closely resembled that here recorded. In spite of laryngeal symptoms during life, Pitts found no changes in the larynx.

The largest number of cases occurred in an epidemic in Christiana in 1919 when there were 32 examples of umbilical diphtheria. Comby[4] reviewing these cases divides them into three groups in order of severity:—(1) No clinical evidence of diphtheria; only proven on culture. (2) Limited ulceration around umbilicus covered with caseous deposit. (3) Widespread inflammation with œdema, necrosis and false membrane formation. Montgomery[5] reports a case with detailed post-mortem findings and a full bibliography.

Case report.

The clinical and pathological records of the present case of umbilical diphtheria are as follows:—

D. V., male, was admitted to hospital at 17 days old suffering from a sceptic umbilicus provisionally diagnosed as erysipelas.

The child's birth had been normal in every respect. The nurse had tied the cord, which had dropped off on the fourth day. On the 14th day the abdominal wall around the umbilicus was said to be red and raw. The nurse called and reported that she thought an abscess was going to form, and although the red area was small it looked as though it might spread. Three days latter (17th day) the child was admitted to hospital.

The patient was the youngest of eight children. Four of these had been removed to a fever hospital with faucial diphtheria during the six weeks preceding the patient's birth. Diphtheria was rampant in the district at the time. The last of of the children to be sent away was removed on the day of this patient's birth.

On admission the child did not appear to be ill. It was well nourished and the temperature and pulse rate normal. A purulent exudate was oozing from the umbilicus which lay at the base of a crater one-tenth to one-eighth of an inch in depth, filled with a yellowish green slough, streaked with dark brown blood. Stretching for half an inch around was a punctate greyish white area dotted with small red spots, and beyond this was a further ring of brawny red skin.

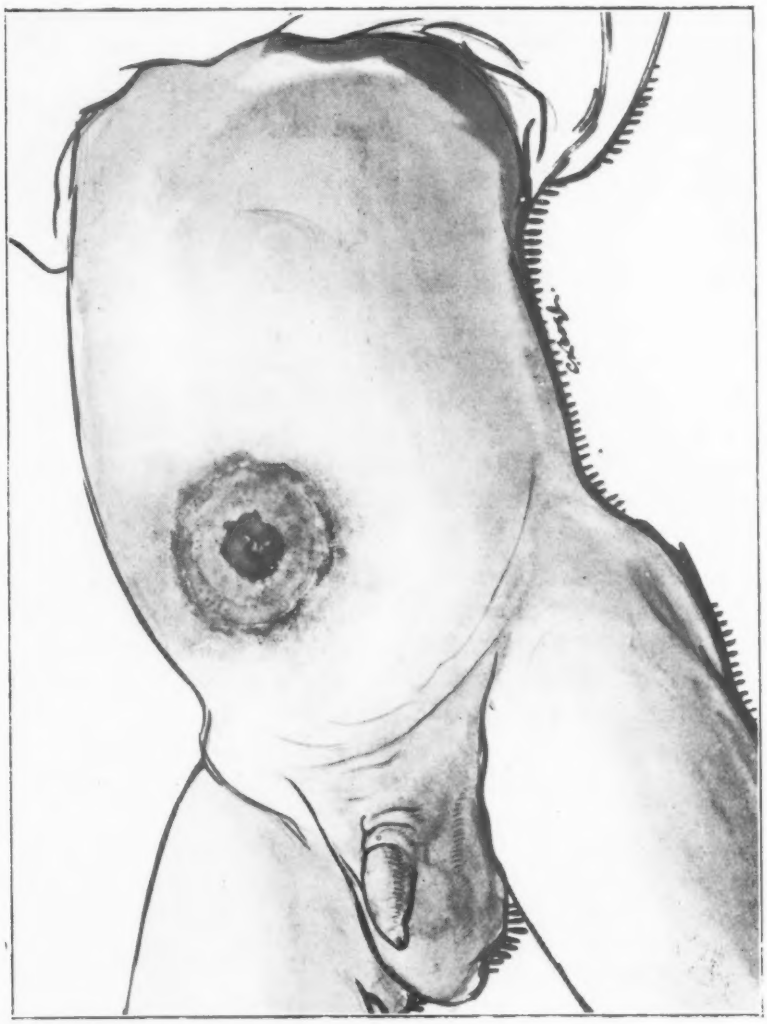

FIG. 1. From a photograph of a painting. The central crater $\frac{1}{10}$th to $\frac{1}{8}$th-in. in depth, showed a yellowish green slough. Round the crater was a yellow area showing many discreet red spots. The edge of the lesion was bright red, fading off into flushed skin.

COURSE. On the day after admission the temperature rose to 100·6° F. but then settled gradually to normal. For four days the peri-umbilical inflammation spread over the abdomen in spite of vigorous local treatment and then began to recede. The umbilicus and crater remained filled with slough.

Swabs were taken from the umbilicus with a view to identifying the infecting organism and throat swabs were also taken in view of the diphtheria history in the

family. The throat and nasal swabs were negative, but from the umbilicus Klebs-Loeffler bacilli were grown, in pure culture. They conformed to the normal carbohydrate fermentation tests and were very virulent to a guinea-pig. The patient was transferred to the North Western Fever Hospital where he died suddenly two days after admission, the 12th day of the illness.

POST-MORTEM EXAMINATION (performed by Dr. Mair). The child was well nourished and of normal size. There was a large ulcer at the umbilicus, 1½ by 2 inches in extent, with necrosis and surrounding inflammation.

Macroscopically all the organs were quite normal. The fauces and nares were quite clean, and swabs taken from them post mortem showed no diphtheria bacilli. The umbilical swabs were again positive. The ulcer had a very indurated base, the induration extending right down to the peritoneum. The peritoneal cavity showed a little free fluid. The umbilical vein was normal. The heart muscle was slightly pale. The adrenals shewed some hæmorrhages.

Microscopically there was no abnormality of the heart muscle, but the adrenals showed intense congestion of the medulla.

Discussion.

Diphtheria occurring apart from the nasopharynx is a very unusual occurrence and is frequently fatal owing to the false membrane not being recognized as diphtheritic in origin. Umbilical diphtheria occurs in the newborn and in infants up to three weeks of age. Comby[1] believes that at certain times diphtheria shows a tendency to attack unusual parts of the body, as in the Christiana outbreak of 1919. Of the other 30 authentic recorded cases many of the earlier ones were fatal, but those occurring in more recent times have been treated with anti-toxin and have recovered. In the present case diphtheria was not considered in the original diagnosis, the appearance being that of a severe cellulitis with sloughing. Actually it falls into the second group recorded above. The main features to be used as a guide in the diagnosis of umbilical diphtheria would appear to be:—

(a) The well nourished appearance of the child who is sucking well and is putting on weight normally.

(b) An inflamed umbilicus with false membrane formation.

(c) A normal temperature almost throughout the disease, quite out of proportion to the severity of the umbilical lesion which, if it were coccal, should be associated with fever; and

(d) Confirmation by bacteriological examination which should be sought in every infection of the umbilicus, particularly in children during the first month of life.

The treatment of these cases is the early administration of serum intramuscularly, to combat the toxæmia and prevent the onset of cardiac or neurological complications. In the case reported the diphtheritic nature was not recognized early enough to save the patient's life.

Summary.

A case of umbilical diphtheria, confirmed by bacteriological examination, is recorded and the points of differential diagnosis are discussed.

We should like to thank Mr. Eric Lloyd under whose care the patient was, for permission to publish the case, and Mr. Charles Keogh for his illustration.

REFERENCES.

1. Löwenstamm, *Med. Chir. Centrabl.*, Vienna, 1878, XIII, 89.
2. Toch, S., *Prag. med. Wchnschr.*, Prague, 1896, XXI, 409.
3. Pitts, B., *Lancet*, London, 1897, i, 953.
4. Comby, J., *Arch. de méd. d. enf.*, Paris, 1921, XXIV, 437.
5. Montgomery, J. C., *Am. J. Dis. Child.*, Chicago, 1930, XL, 968.

EFFECT OF AMMONIUM CHLORIDE ADMINISTRATION ON METABOLISM IN INFANTILE TETANY AND RICKETS

BY

NOAH MORRIS, M.D.,
and
OLIVE MacRAE, M.D.

(From the Department of Pædiatrics, Glasgow University, and the Biochemical Laboratory, Royal Hospital for Sick Children, Glasgow.)

For many years various opinions have been expressed as to disturbances in acid-base equilibrium in rickets and infantile tetany. The view that rickets is essentially a condition of acid poisoning was promulgated many years ago and some workers[1] still hold this view. Recently György[2] has expressed the opinion that a state of acidosis, while not necessarily the fundamental feature, is certainly associated with rickets, and that calcification is prevented by the increased acidity of the bone-forming tissues. With reference to this latter statement, however, Bosanyi[3] found that the pH of rachitic cartilage was more alkaline than the normal, being 7·6 in the former as compared with 7·2 in the latter. Most efforts to obtain direct proof of change in the acid-base equilibrium of the blood or tissues have met with equivocal results, and from the evidence indirectly obtained widely varying conclusions have been drawn. Schabad[4] maintained that the very low urinary excretion of lime and phosphorus in the early stage of rickets was against the theory of increased acid production. Recent investigations in general support this conclusion. Zucker, Johnston and Barnett[5] found that in rats a rachitic condition supervened much more quickly, and to a more marked degree, when the diet was less acid-forming in nature. Thus the substitution of calcium chloride for calcium lactate in a typical rachitic dietary led to the development of a milder type of rickets. Similarly, the addition of 2 per cent. ammonium chloride to the diet prevented rickets in rats, whereas the administration of 2 per cent. sodium bicarbonate even to a well-balanced diet led to marked rickets. Hess[6] found that when rickets was induced with a diet containing 11·5 times as much calcium as phosphorus, the administration of cod-liver oil or irradiated ergosterol, or exposure to ultra-violet light, only produced healing of the rachitic state when there was an excess of acid over basic elements in the diet, as occurred when calcium chloride was substituted for calcium carbonate in equi-molar amounts. On the other hand, Samuel and Kugelmass[7] report experiments on rats in which rickets developed much more markedly on diets free of vitamin D when there was an excess of acid elements.

The urinary excretion of acid and ammonia in rickets has been determined by several workers. Hodgson[8] in 13 patients found an increase in the renal output of both acid and ammonia: Burgess and Osman[9] also reported an increased excretion of ammonia. Freudenberg and György[10], while confirming the increased output of ammonia, found that in some cases the urine was neutral or even alkaline.

Most workers are now agreed that the excessive loss of calcium and phosphorus in the fæces in rachitic conditions is the result, not of increased excretion through the gut-wall, but of defective absorption. The reaction of the alimentary tract has frequently been investigated during the past decade. McClendon[11] and his co-workers in 1919 by direct electrometric investigation showed that normally the reaction of the whole of the small intestine in dogs and cats is on the acid side of neutrality. A year later they reported results indicating that in man the contents of the duodenum and jejunum have normally a pH below 7·0. In 1927 Lloyd Arnold[12] confirmed these findings in dogs. As far back as 1917 Schloss[13] pointed out that the reaction of the fæces was definitely alkaline in the active stage of rickets, and tended to become acid in the healing phase. Redman[14] noted a certain correlation between the mineral content and pH of the fæces of rachitic children thus confirming the observations of Schloss. Experimentally it has been shown in rats that the active stage of rickets is accompanied by a definite alkaline reaction of the fæces, while during the process of healing induced by cod-liver oil or ultra-violet light there is a definite increase in acidity (Zucker and Matzer[15], Jephcott and Bacharach[16], etc.). Direct determinations of the pH of the contents of the small intestine in dogs show that on a rickets-producing dietary (Mellanby's) the reaction changed from acid to alkaline, while addition of cod-liver oil to the food or exposure to ultra-violet light produced a return to an acid reaction (Grayzell and Miller[17]). Similar findings are reported by Tisdall and Price[18] in rats in which rickets had been produced. The consistency of these results provides almost conclusive proof that there is an actual change in the pH of the intestinal contents to the alkaline side in the active phase of rickets. While such a change in reaction would account for the defective absorption of calcium and phosphorus it is not sufficient to explain all the manifestations of the rachitic condition. Thus it has been shown experimentally that simple deprivation of lime, such as would occur if the sole abnormal factor were defective absorption, leads not to rickets but to osteo-porosis.

Present investigation.—The following investigation was undertaken to determine the effect of the administration of an acid-producing salt on the mineral metabolism in rickets and tetany. Ammonium chloride was the substance chosen to produce the acidosis, chiefly because in the gut it is neutral and therefore it was hoped that the influence of acidosis on the tissues could be studied without any direct action on the intestinal contents. It has already been shown by Gamble[19] and his co-workers and ourselves[20] that

calcium and phosphorus play an important part in dealing with a sudden excess of acid radicle in the tissues, at any rate until the ammonia formation has increased to such a pitch as to neutralize the extra acid. If the rachitic condition is accompanied by a state tending to acidosis it seems natural to expect that the organism will be less capable of dealing with the extra acid, especially when it is remembered that the bones are deficient in calcium and phosphorus.

The effect of ammonium-chloride administration on the calcium, phosphorus and chlorine metabolism was studied in four children who showed evidence of rickets. In three, in addition to a marked degree of active rickets shown by radiogram, there were present signs of tetany manifested by Chvostek's sign and in one laryngismus was also noted. In the fourth child the radiogram indicated that spontaneous healing was taking place during the period of the investigation. Two metabolic studies of seven days' duration were made in each patient. The diets were kept constant for three days prior to the commencement of the investigation and remained unchanged until the completion of the studies. In the second of the two ' metabolic ' periods ammonium chloride was given in one gramme doses five times daily.

Clinical features.—No clinical signs of acidosis were manifest during the period of ammonium-chloride administration. In Case 1, 5 grm. of ammonium chloride was given daily for 38 days without any obvious clinical indication of acidosis. In a previous investigation[20] we noted that in the normal child a similar dosage of ammonium chloride was also without apparent clinical effect, and we attributed this result to the fact that the acid-producing salt when given in small amounts frequently, and not in one massive dose daily, allowed the metabolic processes to deal with the influx efficiently and thus prevent manifest disturbance. It is clear that in active rickets the power of the individual to deal with acid is at least as good as normal so far as the prevention of clinical manifestations of acidosis is concerned. During the administration of the ammonium chloride Chvostek's sign disappeared in all the cases. In Case 3, the laryngeal spasm also disappeared during the administration of ammonium chloride, but both it and Chvostek's sign returned on the day after the ammonium-chloride ingestion ceased, although in the other two patients there was no return of any sign of tetany.

Perhaps the most remarkable clinical feature noted was the appearance of healing in the radiogram of Case 1 after 38 days' administration of ammonium chloride although the environmental and dietetic conditions remained constant throughout this period. A series of weekly radiograms (Table 6, p. 57) indicate that the healing became apparent two weeks after the initiation of ammonium-chloride ingestion, and gradually increased until at the end of 38 days it was definite, although not nearly so marked as that which occurs with vitamin-D preparations or ultra-violet light. The fact

that healing can take place during the administration of an acid-producing salt is in itself strong evidence against the view that there is in rickets a shift of acid-base equilibrium to the acid side. It may be urged that this patient was suffering from tetany. Nevertheless the occurrence of healing after the disappearance of Chvostek's sign indicates that in rickets the deposition of calcium can take place during the ingestion of a great excess of acid-producing substance.

Blood chemistry (Table 1).—The serum calcium which was abnormally low in all three patients (Cases 1, 2 and 3) with rickets and tetany showed a marked increase during ammonium chloride administration although the

TABLE 1.

CHANGES IN CHEMICAL COMPOSITION OF BLOOD.

Case No.	Stage.	Calcium mgrm. %	Phosphorus mgrm. %	CO_2 Vol. %	N.P.N. mrgm. %
1	Before NH_4Cl administration	—	3·0	50·7	—
	3 weeks on NH_4Cl	6·1	3·4	40·3	39·8
	4 ,, ,, ...	6·5	4·8	—	—
	5 ,, ,, ...	7·4	4·2	37·8	40·9
	1 week after NH_4Cl stopped	6·9	2·8	59·6	31·6
2	Before NH_4Cl administration	7·6	5·6	55·6	34·8
	1 week on NH_4Cl	8·0	3·6	44·7	44·5
3	Before NH_4Cl administration	7·6	6·2	52·5	36·3
	1 week on NH_4Cl	8·9	4·6	41·4	43·1

normal level was not quite reached while the patients were under observation. The inorganic phosphorus content of the serum which was high in two patients (Cases 2 and 3) before the commencement of the ammonium chloride fell during that period, while in the third (Case 1), where it was initially low, an increase was noted for three weeks followed by a slow decline in its value. The total CO_2 of the blood was lowered during the ammonium chloride administration while the chlorine tended to rise in value and the non-protein nitrogen showed no change. Generally it may be said that the changes in blood chemistry following the administration of ammonium chloride are the same in rachitic patients as they are in normal children. Further, it may be said that the results of blood analysis indicate the presence of what van Slyke has termed a compensated acidosis, just as occurs in healthy children under similar conditions,

Metabolism.

It will be convenient first to summarize the metabolic results for each substance individually and thereafter to correlate the various findings.

Volume, titratable acidity and ammonia of urine (Table 2).—There was a slight increase in urinary volume in two of the cases during the ammonium-chloride period. In Case 3 the amount of urine was only half of that of the control period and in Case 4 (early healing) it was reduced by about one-tenth. The titratable acidity of the urine during the ammonium-chloride period was in none of the cases as greatly increased as it is in the

TABLE 2.

SHOWING URINARY OUTPUT OF WATER, TITRATABLE ACID, AMMONIA AND CHLORIDE.

Case.	Period.	Volume c.cm.	T.A. c.cm. N/10.	Ammonia c.cm. N/10.	NaCl. grm.
1	1st. Normal. 6 days	1800	211·6	1224·4	5·780
	2nd. NH_4Cl. 6 days	1860	450·0	1723·2	12·028
2	1st. Normal. 7 days	5485	711·6	2362·0	12·5341
	2nd. NH_4Cl. 7 days	5510	1424·0	5496·2	39·0678
3	1st. Normal. 7 days	4290	404·8	1042·8	10·6307
	2nd. NH_4Cl. 7 days	2355	162·0	3591·0	18·8400
4 Healing rickets	1st. Normal. 7 days	4030	787·6	1584·8	11·5673
	2nd. NH_4Cl. 7 days	4849	1516·0	5515·0	41·7650

normal child: in Case 3 there was an actual decrease. There was a normal rise in the ammonia output in all except Case 1, where the increase was much less than normal.

Chlorine (Table 2).—The retention of chlorine in these four subjects shows a distinct variation from normal both in the control and ammonium-chloride periods. In normal children on an adequate milk diet the retention of chlorine varies from zero to about 12 per cent. of the intake. In all the four patients studied the chlorine retained amounted to over 12 per cent. of the intake. In Case 1 36·6 per cent. of the chlorine ingested over a six-day period was not excreted in the urine. Practically no chlorine was found in the fæces and as there was no noticeable perspiration, it is unlikely that the diminished urinary excretion was due to excess being passed out in the sweat. When the results of the ammonum-chloride periods are examined this tendency to retain chlorine becomes even more apparent. In normal

children over 80 per cent. of the extra chlorine ingested is found in the urine. In the present series the percentage excreted fell far below that figure, except in Case 4 in which the rickets was healing and in whom the percentage excreted amounted to 78·9 per cent. of the extra intake.

Calcium and phosphorus (Tables 3 and 4).—In all instances administration of ammonium chloride led to an increased urinary output of lime and phosphorus. The increase was very marked in the case of healing rickets particularly in the output of calcium which was increased fourfold: in the others the increase was slight. The fæcal output of both lime and

TABLE 3.

SHOWING INTAKE, FÆCAL AND URINARY OUTPUTS AND RETENTION OF CALCIUM AND PHOSPHORUS (IN GRAMMES). (7-DAY PERIODS).

Case.	Period.	Intake.		Output.				Retention.			
				Fæces.		Urine		Total.		Daily per kgrm.	
		CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO	P_2O_5	CaO mgrm.	P_2O_5 mgrm.
1	1. Normal	8·208	10·80	6·915	5·391	·067	3·696	1·226	1·803	30	44
	2. NH_4Cl	8·208	10·80	6·293	4·644	·084	3·740	1·831	2·416	45	59
2	1	15·12	21·168	13·837	11·408	·116	7·772	1·167	2·996	12	21
	2	15·12	21·168	9·743	8·419	·205	8·436	5·172	5·321	57	47
3	1	12·60	17·64	9·984	12·355	·092	2·320	2·524	3·805	37	44
	2	12·60	17·64	9·148	11·616	·146	2·754	3·306	4·110	50	57
4	1	12·60	16·38	7·076	4·946	·176	6·512	5·348	3·922	75	55
Healing	2	13·02	16·80	9·284	7·346	·713	7·676	3·023	1·778	41	17

phosphorus was increased in Case 4 (healing), as a result of rise in fæcal weight and percentage of minerals in the fæces. In the patients with active rickets the output of lime and phosphorus in the fæces was greatly reduced; in Case 1 the reduction was due both to a fall in fæcal weight and in percentage content, while in Cases 2 and 3 the main factor was the reduction in the percentage content of lime and phosphorus of the fæces. It is of interest to note that in the patient (Case 3) who had the signs of tetany most marked, the phosphorus content of the fæces was very high and the combined fatty acids very low in both periods. The most striking difference between the behaviour of the patient with active rickets and that of the normal child or one with healing rickets is the increased retention of calcium and phosphorus in the former during ingestion of ammonium chloride and the decrease in the later. This is in accord with the radiographic evidence of definite healing in Case 1 already mentioned.

TABLE 4.

SHOWING ASH, CALCIUM, PHOSPHORUS AND FAT CONTENT OF FÆCES (7-DAY PERIODS).

Case	Condition.		Period 1 (Normal). Total quantity in fæces grm.	Period 1 (Normal). % in fæces	Period 2 (NH_4Cl). Total quantity in fæces grm.	Period 2 (NH_4Cl). % in fæces.
1	Active rickets and tetany	Fæcal weight ...	46·1	—	43·40	—
		Ash	—	31·4	—	29·7
		CaO	6·915	15	6·293	14·5
		P_2O_5	5·301	11·5	4·644	10·7
		Total fat	19·929	43·23	18·857	43·45
		Combined fatty acids	15·314	33·22	12·551	28·92
		Free fatty acids ...	3·298	7·155	5·859	13·50
		Neutral fat	1·316	2·855	0·447	1·03
2	Active rickets and tetany	Fæcal weight ...	73·6	—	52·95	—
		Ash	—	40	—	40
		CaO	13·837	18·8	9·743	18·4
		P_2O_5	11·408	15·5	8·419	15·9
		Total fat	20·939	28·45	17·542	33·13
		Combined fatty acids	12·622	17·15	10·521	19·87
		Free fatty acids ...	5·961	8·1	5·004	9·45
		Neutral fat	2·355	3·2	2·017	3·81
3	Active rickets and tetany	Fæcal weight ...	62·4	—	72·6	—
		Ash	—	45	—	45
		CaO	9·984	16·0	9·148	12·6
		P_2O_5	12·355	19·8	11·616	16·0
		Total fat	17·515	28·07	18·411	25·36
		Combined fatty acids	1·622	2·60	1·365	1·88
		Free fatty acids ...	12·299	19·71	10·781	14·85
		Neutral fat	3·594	5·76	6·265	8·63
4	Healing rickets	Fæcal weight ...	36·1	—	45·07	—
		Ash	—	38·2	—	42·1
		CaO	7·076	19·6	9·284	20·6
		P_2O_5	4·946	13·7	7·346	16·3
		Total fat	6·743	18·68	7·310	16·22
		Combined fatty acids	4·498	12·46	4·439	9·85
		Free fatty acids ...	0·975	2·7	1·767	3·92
		Neutral fat	1·270	3·52	1·104	2·45

Discussion.

The following differences are to be noted in the reaction of the rachitic patient to ammonium chloride from that of the normal child (Table 5).

1. There is an increase in the retention of lime and phosphorus in active rickets. When the rickets is healing ammonium chloride leads to a decrease in the retention of minerals as in health.

2. A much smaller proportion of the extra chlorine ingested is excreted by the rachitic than by the normal individual.

3. The increase in the urinary excretion of titratable acid and ammonia is not so marked in active rickets as in health or healing rickets.

TABLE 5.

COMPARISON OF THE METABOLIC REACTIONS OF NORMAL AND TETANY-RICKETS GROUPS TO ACIDOSIS PRODUCED BY AMMONIUM CHLORIDE.

		Normal.	Healing rickets.	Tetany-rickets.
Urine	Increase in titratable acidity	+ +	+ +	+
	Increase in ammonia	+ +	+ + +	+
	% of excess chlorine excreted	+ + +	+ +	+
	Excretion of CaO	+	+ +	+
	Excretion of P_2O_5	+	+	+
Fæces	Excretion of CaO	+	+	—
	Excretion of P_2O_5	+	+	—
Retention ...	CaO	—	—	+
	P_2O_5	—	—	+

The increased retention of lime and phosphorus following ammonum-chloride administration in active rickets is in marked contrast to what occurs in health and healing rickets. The use of acid-producing salts therapeutically as a softener of bones is well-known. Ammonium chloride was chosen in this study as an acid-producing substance because of its neutrality in the gut. Nevertheless the possibility must be conceded of its being able to decrease the pH in the intestine secondarily by its effect on the composition of the body fluids. In this way absorption of the mineral elements would be facilitated. It may further be urged that the increased retention resulting from ammonium-chloride administration is due to the fact that the mineral-starved bones utilize so much of the extra lime and phosphorus absorbed that the slight increase in the amount excreted is completely overshadowed. This contention cannot be upheld in view of the results recorded in the case of healing rickets. The mineral retention was here reduced during the

ammonium-chloride period just as in the normal child in spite of the fact that, healing having just commenced, there was still osteo-porosis shown in the radiogram at the time of the study. To explain the effect of ammonium chloride in increasing the retention of lime and phosphorus in active rickets, it therefore seems necessary to assume that some change has been effected enabling the tissues of the patient with active rickets to fix calcium and phosphorus. If this assumption be granted the corollary must be drawn that in addition to a probable defect in the absorption of minerals from the intestine there also exists in or around the tissues a condition which prevents the fixation of lime and phosphorus. As soon as healing commences, although the bones are still very defective in mineral content, the state of the tissues is such that administration of ammonium chloride leads to increased mineral excretion just as occurs in the healthy child. The fact that an acid-producing salt like ammonium chloride can during the active stage of rickets lead to an increased fixation of lime and phosphorus makes it highly improbable that in active rickets acidosis is either a causal or an associated factor. In this connection two other findings in the present investigation are of importance.

1. Subnormal increase in urinary acidity. This might at first glance be attributed to the diminished output of urinary phosphorus providing a smaller amount of phosphate for conversion from the mono- to the di-hydrogen salt. This explanation, however, is not satisfactory since the increase in the renal excretion of phosphorus during ammonium chloride ingestion is high relative to the increase in titratable acid. It would appear, therefore, that in these cases the tendency is for acids to be retained.

2. Subnormal increase in the excretion of chlorine. Defective renal function might be suggested as the explanation of this finding. There was, however, in none of the cases any impairment of kidney function. It is true that the ammonium output did not rise to the extent found in healthy children after ammonium-chloride administration; but this is more readily explained on the assumption that acid being retained, there was obviously no need for as much extra alkali to be formed. Further, if in active rickets there is relative excess of fixed base that excess will be used in preference to ammonia for the transport of acid.

The fact that an acid radicle such as chlorine is retained to an extent far exceeding the normal is strong supporting evidence of the view that if there is any change in acid-base equilibrium in active rickets that change is towards the alkaline and not the acid side.

In connection with the retention of chlorine it is of interest to mention the findings of Morris, Watson and Morris[21] in experimental tetany induced by thyro-parathyroidectomy or injection of guanidine. During both the latent and active periods of these types of tetany there occurred a very marked retention of chlorine. Analysis of the tissues showed that the tissue content of chlorine was markedly increased. Further, there was noted a

relationship between the amount of chlorine retained, the quality and amount of protein breakdown, and the development of convulsions. When the protein katabolism was in great excess relative to the amount of available chlorine, active tetany ensued. This suggests an explanation of the effect of high-protein intake in the form of meat in the conversion of a latent to an active tetany. It will be seen, therefore, that our results in the three children with tetany and rickets corroborate these experimental findings.

The clinical findings show that ammonium chloride did not in any way aggravate the rachitic condition. As in normal individuals receiving similar dosage, there was no apparent symptom of acidosis. It is admitted that in three patients there was tetany, in which condition the beneficial action of acid-producing substances has long been known. Nevertheless, radiographic evidence of healing was marked in the one patient who was given ammonium chloride for a prolonged period. And in the other two subjects of tetany, although all signs disappeared within two days, continued administration of ammonium chloride did not lead to any untoward manifestation. If rickets were accompanied by an increased acid formation the accumulation of acid resulting from ammonium chloride should lead to an aggravation of the condition, or at least prevent healing. The clinical, radiographic and metabolic results all show exactly the opposite. It therefore seems justifiable to conclude that there is no tendency to acidosis in rickets.

Shohl[22] and his colleagues have recently published results showing that in rats made rachitic on a high-calcium low-phosphorus diet (Steenbock 2965) serum analyses indicate a state of the acid-base equilibrium bordering on alkalosis. Thus, although there is no conclusive evidence in the work detailed in this paper that a condition of alkalosis exists, it is tempting to draw this conclusion.

Summary.

The administration of ammonium chloride to three patients with active rickets and latent tetany, and to one patient with early healing rickets produced no apparent signs of acidosis.

In the tetany-rickets group there was a definite increase in the retention of calcium and phosphorus, a subnormal increase in the output of titratable acid and a marked retention of the excess chlorine. In healing rickets there was a definite decrease in the retention of calcium and phosphorus, but a retention of the excess chlorine slightly above normal.

One patient who was given ammonium chloride over a period of five weeks showed radiographic and metabolic evidence of healing, although the dietetic and environmental conditions were kept unchanged.

The findings are discussed and it is concluded that there is no evidence of any tendency to acidosis in rickets.

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TABLE 6.

PROGRESS OF HEALING IN CASE I AS INDICATED BY RADIOGRAMS.

(R.M., aet. 2 years, 1 month).

Date.	
8.5.29	Admitted to hospital.
9.5.29	X-ray of wrist: active rickets.
16.5.29	,, ,, I.S.Q.
23.5.29	,, ,, I.S.Q.
1.6.29	,, ,, I.S.Q.
6.6.29	,, ,, I.S.Q.
18.6.29	,, ,, I.S.Q.
19.6.29	Commencement of administration of NH_4Cl 1 grm. 5 times daily.
29.6.29	X-ray of wrist: I.S.Q.
30.6.29	Administration of NH_4Cl ceased.
10.7.29	X-ray of wrist: definite signs of early healing.
24.7.29	,, ,, ? further advance in healing process.
31.7.29	Administration of NH_4Cl 1 grm. five times daily again started.
12.8.29	X-ray of wrist: definite advance in healing process.
22.8.29	,, ,, further healing.
29.8.29	,, ,, very slow healing progressing.
8.9.29	Administration of NH_4Cl ceased.
9.9.29	X-ray of wrist: further healing.

REFERENCES.

1. Pritchard, E., *Brit. Med. J.*, London, 1923, i, 887.
2. György, P., *Ergebn. d. inn. Mediz. u. Kinderheilk.*, Berlin, 1929, XXXVI, 752.
3. Bosanyi, A., *Jahrb. f. Kinderheilk.*, Berlin, 1927, CXVII, 240.
4. Schabad, *Arch. f. Kinderheilk.*, Stuttgart, 1910, LIII, 380; 1910, LIV, 83.
5. Zucker, T. F., Johnson, W. C., & Barnet, M., *Proc. Soc. Exp. Biol. & Med.*, N.Y., 1922, XX, 20.
6. Hess, A. F., Weinstock, M., Rivkin, H., & Gross, J., *Ibid.*, 1929, XXVII, 140.
7. Samuel, E. L., & Kugelmass, I. N., *Amer. J. Dis. Child.*, Chicago, 1930, XXXIX, 687.
8. Hodgson, A., *Lancet*, London, 1921, ii, 945.
9. Burgess, N., & Osman, A. A., *Ibid.*, 1924, i, 281.
10. Freudenberg, E., & György, P., *Münch. med. Wochen.*, München, 1922, XII, 422.
11. McClendon, J. F., Bessell, F. S., Lowe, E. R., & Meyer, P. F., *J. Amer. Med. Assoc.*, Chicago, 1920, LXXV, 1638.
12. Lloyd, A., *Klin. Wochenschr.*, Berlin, 1927, i, 607.
13. Schloss, E., *Ergeb. d. inn. Mediz. u. Kinderheilk.*, Berlin, 1917, XV, 55.
14. Redman, T., *Biochem. J.*, Cambridge, 1929, XXIII, 256.

15. Zucker, T. F., & Matzner, M. J., *Proc. Soc. Exp. Biol. & Med.*, N.Y., 1923, XXI, 186.
16. Jephcott, H., & Bacharach, A., *Biochem. J.*, Cambridge, 1926, XX, 1350.
17. Grayzell, D. M., & Miller, E. G., *J. Biol. Chem.*, Baltimore, 1928, LXXVI, 423.
18. Tisdall, F., & Price, H. W., *Bull. Johns. Hopk. Hosp.*, Baltimore, 1927, XLI, 432.
19. Gamble, J. L., Ross, S. G., & Tisdall, F., *Amer. J. Dis. Child.*, Chicago, 1923, XXV, 455.
20. Morris, N., & MacRae, O., *Arch. Dis. Childh.*, London, 1930, V, 207.
21. Morris, S., Watson, A. M., & Morris, N., *Biochem. J.*, Cambridge, 1931, XXV, 786.
22. Shohl, A. T., Brown, H. B., Rose, C. S., Smith, D. N., & Cozad, F., *J. Biol. Chem.* Baltimore, 1931, XCII, 711.